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EFFECT OF INJECTION OF NONSPECIFIC PROTEIN ON DIPHTHERIA VIRULENCE TESTS IN GUINEA-PIGS *

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CONTROVERSY CONCERNING THE VALUE OF HORSE SERUM

Bingel,[1] noting that toxic cases of diphtheria, in which the most marked effect might be anticipated from antitoxin treatment, react only slightly, questioned the possibility of nonspecific reaction due to a foreign serum. He treated alternating cases of diphtheria entering the hospital with normal horse serum and with antitoxin. He was unable to see any appreciable difference between the 471 horse serum treated cases and the 466 antitoxin treated cases. The bacilli disappeared after four weeks in 89.6 per cent. of the antitoxin treated cases and in 94.6 per cent. of the horse serum cases. He concluded that the success of the serum therapy in diphtheria was dependent on the larger amount of horse serum used with the larger doses of antitoxin. Perhaps Bingel's results with horse serum may be due to the fact that only 45.7 per cent. of his antitoxin treated cases received antitoxin on the third day, or earlier, while 61.1 per cent. of the horse serum treated cases received injections on the third day or earlier.

This communication of Bingel's led to the most violent criticism. Johannovics [2] considered with astonishment this "bolt from a clear sky," and marshalled statistics to prove that antitoxin was specific, although it has long been granted that it was not so efficient in toxic forms of diphtheria where generalized poisoning occurred before specific serum therapy was started. He questioned the ethics of experimenting on

* Received for publication, Dec. 13, 1920.

* This study was made possible by Grant 49 awarded by the Committee on Scientific Research of the American Medical Association.

1. Bingel, A.: Ueber Behandlung der Diphtherie mit gewöhnlichem Pferdeserum, Deutsch. Arch. f. klin. Med. **125**:284, 1918.

2. Johannovics, G.: Zur Behandlung der Diphtherie mit gewöhnlichem Pferdeserum, Wien. klin. Wchnschr. **32**:220 (Feb. 27) 1919.

patients, and quoted Groer's [3] conclusions that antitoxin-free horse serum may not limit the specific diphtheria toxin effect in man. Then he figured that in 200 cases treated with normal horse serum on the first day, Bingel would have lost seven cases that could have been saved by the use of antitoxin.

Feer [4] tested the value of normal horse serum in mild cases only, giving 13 c.c. of horse serum intramuscularly. These mild cases took longer to clear up than the more severe antitoxin treated cases, and in six cases it became necessary to give antitoxin in addition to horse serum. In no case with horse serum treatment was there the favorable red line of demarkation on the mucous membranes, which was frequently observed with antitoxin treated cases.

Friedberger,[5] using diphtheria bacilli instead of diphtheria toxin, gave guinea-pigs about five times the fatal dose of a known culture of *B. diphtheriae* isolated from a fatal case. He then attempted to cure them with horse serum, using an intravenous injection of 0.5 c.c. or less of normal horse serum. He found that animals with an overdose of horse serum died earlier than animals with a small dose or than animals without any horse serum. His series was small, the table showing only twenty animals for two strengths of antitoxin, two sets of horse serum, and two control pigs without either horse serum or antitoxin treatment. He concluded that in guinea-pigs highly virulent diphtheria infections were not affected by normal horse serum in large doses, while antitoxin had a prompt effect.

Kolle and Schloszberger,[6] experimenting on animals, decided that normal horse serum therapeutically did not act as antitoxic serum in guinea-pigs. They used diphtheria toxin and attempted to cure 196 pigs with normal horse serum. Of these 48 died the first day after the toxin injection before any treatment was given, and of 53 treated pigs only 2 lived, as compared to the 95 pigs with antitoxin treatment, of which 51 recovered and 44 died. They gave three times the fatal dose of toxin, and in both horse serum and antitoxin treated pigs there were extensive areas of necrosis. They found that with both living diphtheria organisms and diphtheria toxin there was a slight curative action in large doses of horse serum when the time elapsing

3. Groer: Zur Frage der Bedeutung aspizifisher ergotroper Wirkungen des Serums bei der Heilserum-therapie der Diphtherie, Ztschr. f. d. ges. exp. Med. **7**:171, 1918.

4. Feer, E.: Zur Behandlung der Diphtherie mit gewöhnlichem Pferdeserum, München. med. Wchnschr. **66**:343 (March 28) 1919.

5. Friedberger, E.: Hat das normale Pferdeserum einen Einfluss auf die experimentelle Infection des Meerschweinchens mit Diphtherie-bazillen, Berl. klin. Wchnschr. **56**:151 (Feb. 17) 1919.

6. Kolle, W., and Schloszberger, H.: Zur Frage der Heilwirkung des Diphtherieserums, Med. Klin. **15**:1, 83, 1919.

before the injection was not more than from four to six hours postinfection.

This outlines the controversy which led to the experiments reported in this paper. There is no question at all concerning the specificity of antitoxin, in large doses, in diphtheria, but what is the effect of foreign protein injection on the results of the virulence tests for diphtheria in guinea-pigs? Can it be substituted in an emergency for antitoxin?

METHOD USED FOR VIRULENCE TESTS

At the time when this work was started our laboratory was engaged in an intensive study of a large series of diphtheria strains obtained from different sources, and my work is testing the virulence of the strains. We use the intracutaneous or intradermal test outlined by Zingher and Soletsky.[7] We modify the method slightly so that our standard method consists in shaving the abdomen of a guinea-pig, making room for 6 or 8 intracutaneous tests. Two pigs constitute the routine series; one, the test pig, receives the intradermal injection of 0.15 c.c. of a suspension of a twenty-four hour growth on a Loeffler's blood serum tube in 15 c.c. of sterile 0.9 per cent. sodium chlorid solution. The other pig, the control pig, receives the same intradermal injections immediately following the intracardial injection of 250 units of diphtheria antitoxin which has a horse serum volume of from 0.25 to 0.50 c.c. The strains of *B. diphtheriae* are in pure culture. Shumway[8] has determined that a twenty-four hour growth on Loeffler's blood serum suspended in sterile 0.9 per cent. sodium chlorid solution gives more uniform results than a forty-eight hour bouillon culture. I have also determined that an intradermal injection of 0.15 c.c. gives reactions which are more easily read than an injection of 0.25 c.c., where pressure necrosis may become a complicating factor.

The intradermal test gives a reaction that is accurate. The circumscribed necrosis may be measured in size, in rate of development and in time of duration. If nonspecific protein therapy has an effect on diphtheria virulence we have here an easy method for determining that effect.

NONSPECIFIC PROTEINS USED

Two nonspecific proteins are in common therapeutic use for man; one, typhoid vaccine; the other, normal horse serum. Consequently, these are selected for the tests and checked, finally, with a single egg-white series. The dosage is purposely made large; the typhoid vaccine

7. Zingher, A., and Soletsky, D.: An Economical Intracutaneous Method for Testing the Virulence of Diphtheria, J. Infect. Dis. **17**:454, 1915.

8. Shumway, V.: Unpublished Thesis for M.S. Degree, 1919, State University of Iowa Library, Iowa City.

is the ordinary commercial vaccine standardized so that 1 c.c. contains one billion dead typhoid organisms. The horse serum is obtained in 20 c.c. vials, and all the material used came from one lot, No. 29554-9892 F, with an expiration date of Oct. 22, 1920. Concerning this E. Lilly & Sons state in a letter dated July 14, 1920: "The horses delivering this serum have never been subjected to any immunizing processes," and, "we have very accurate records on all horses used for the production of normal horse serum." The guinea-pigs are standard sized pigs all closely approximating 250 gm. in weight, which have never been used for any laboratory tests.

THE METHOD OF INJECTING FOREIGN PROTEIN AND ANTITOXIN

For three years our laboratory has used the intracardial method for obtaining blood from rabbits and guinea-pigs and for the injection of antitoxin in virulence tests. The mortality is very low in the hands of one with a little experience, no anesthetic is required, and the method is more rapid and shows fewer complications than occur with the use of the jugular vein of the guinea-pig for intravenous injection. Among more than 150 pigs receiving intracardial injections there were two deaths, both due to penetration of the auricle instead of the ventricle, with a resultant hemorrhage into the pericardium. There are no cases of fatal embolism.

My method is to tie the pig on an animal board, feel for the apex beat with the most sensitive finger tip, just to the left of the sternum. This is usually the intercostal space on a line with the axilla. With a sterile needle enter this space, going almost vertically down. Sometimes the sense of touch tells one when the ventricle is entered, but the safest guide is the appearance of blood in the syringe on slight withdrawal of the piston. The volume of the foreign protein injected is 0.25 c.c. volume of typhoid vaccine and antitoxin, from 0.5 to 1 c.c. volume of horse serum and of egg white. This is injected rapidly to avoid any chance of the needle slipping from the heart cavity.

EFFECT OF THE INTRACARDIAL INJECTION OF TYPHOID VACCINE ON THE INTRACUTANEOUS TEST

Table 1 shows the effect of an intracardial injection of 250 million dead typhoid organisms immediately preceding the intracutaneous injection of 0.15 c.c. of a suspension of a twenty-four hour growth on Loeffler's blood serum in 15 c.c. of sterile isotonic salt solution.

This shows clearly that the intracardial injection of typhoid vaccine followed immediately by the intradermal injection of cultures of *B. diphtheriae* increases the sensitiveness of the virulence test. The necrosis occurs, as a rule, earlier, the reaction is more marked, usually larger

TABLE 1.—Effect of Intracardial Injection of 250 Million Dead Typhoid Bacilli Immediately Preceding the Injection of B. Diphtheriae Cultures Intracutaneously, Compared with Test Pigs and Antitoxin Controls

Number and Strain of B. diphtheriae		Antitoxin Control Pig	Test Pig				Typhoid Vaccine Pig			
			First Reaction Noted	Necrosis	Lesion Cleared	Notes	First Reaction Noted	Necrosis	Lesion Cleared	Notes
1	2*	—	12 hours	5th day	12 days	.....	12 hours	2d day marked	12 days	More rapid and marked
2	5	—	36 hours	36 hours	8 days	.....	33 hours	36 hours	13 days	Long duration
3	8*	—	18 hours	48 hours	Killed in 48 hours	.....	18 hours	3d day	Died in 72 hours	
4	12*	—	24 hours	—	Died in 60 hours	.....	24 hours	—	Died in 48 hours	Early death
5	15*	—	16 hours	36 hours	23 days	.....	16 hours	4th day	31 days	Long duration
6	16	—	16 hours	—	4 days	Negative test	16 hours	24 hours	15 days	Positive
7	17	—	21 hours	4th day	8 days	.....	18 hours	—	Died in 48 hours	Early death
8	21	—	16 hours	4th day	23 days	.....	16 hours	38 hours	32 days	Rapid necrosis and long duration
9	25	—	38 hours	62 hours	11 days	.....	36 hours	62 hours	14 days	Long duration
10	26	—	12 hours	—	7 days	Negative test	12 hours	48 hours	7 days	Positive
11	27	—	16 hours	4th day	13 days	.....	16 hours	48 hours marked	14 days	More rapid and marked reaction
12	30†	—	—	—	—	Negative test	—	—	Paralysis lasting 4 days	Negative test
13	31‡	—	16 hours	4th day	10 days	.....	16 hours	4th day	20 days	Long duration
14	32	—	3 days	5th day	7 days	.....	12 hours	48 hours	12 days	More rapid and longer duration
15	34	—	18 hours	— ?	Killed on 3d day	Negative test	36 hours	4th day	Died on 4th day	Positive
16	36	—	12 hours	5th day	12 days	.....	12 hours	2d day	12 days	More rapid
17	38	—	—	—	Killed on 3d day	Negative test	18 hours	3d day	Died on 4th day	Positive
18	39	—	—	—	Killed on 3d day	Negative test	18 hours	3d day	Died on 4th day	Positive
19	122	—	36 hours	5th day	13 days	.....	36 hours	36 hours	—	More rapid
20	140	—	60 hours	60 hours (8 mm.)	12 days	.....	60 hours	60 hours (25 mm.)	Not cleared in 28 days	Larger and longer duration
21	144	—	—	—	—	Negative test	60 hours	5th day	12 days	Positive
22	145	—	36 hours	36 hours (5 mm.)	12 days	.....	60 hours	3d day (10 mm.)	14 days	Larger and longer duration
23	146	—	24 hours	4th day	—	.....	36 hours	36 hours	—	
24	147	—	—	—	—	Negative test	36 hours	36 hours	—	Positive test
25	154	—	24 hours	36 hours	12 days	.....	36 hours	36 hours	—	

* Virulent on subcutaneous test. † Toxin producing strain from Parke Davis. ‡ Park 8.

Twenty-five different strains tested on 54 pigs. All strains tested were morphologically granular types which gave the sugar fermentation tests of true diphtheria.

in size and clears more slowly than the corresponding area in test pigs. In eight strains giving a negative intracutaneous test on the ordinary test pig, the reaction was definitely positive on the nonspecific protein pig receiving typhoid vaccine. The first explanation that suggests itself is that the diphtheria organism is being introduced during the leukopenia stage, when there is a lowered resistance and an increased sensibility so that varying the time of the typhoid injection might alter the result. But intracardial injections made as long as forty-eight hours preceding the intradermal tests do not change the reaction. The difference between the severity of the reactions on the typhoid pigs, the test pigs, and the control pigs is so marked that it is easy to pick out the different series without reference to the card records.

EFFECT OF THE INTRACARDIAL INJECTION OF HORSE SERUM ON THE INTRACUTANEOUS TEST

After testing the virulence of forty different strains with typhoid vaccine, and establishing the increase in the severity and the prolongation of the time of the reaction, horse serum is substituted as the nonspecific protein, 1 c.c. being injected into the heart immediately preceding the intradermal inoculation. The first twelve strains tested showed no reaction at all on the horse serum pigs, not even the hyperemia which is often seen on the antitoxin pigs during the first twelve hours. I was afraid the attendant might have confused the syringes, handing me an antitoxin syringe instead of one containing horse serum, hence these twelve tests were not included in the series, and they were repeated again. The results of the second test are the same as the first. Fifty different strains of *B. diphtheria* are tested. Twenty-five of these on a series of forty-two pigs are reported in Table 2. All these strains of *B. diphtheriae* are granular types giving the fermentation tests of true diphtheria organisms.

This series shows six test pigs with positive intracutaneous tests while the corresponding horse serum pigs show no reaction. Table 2 is also of interest because of the large number of typical diphtheria strains that are avirulent on the initial tests. In only one instance is there a positive reaction on the horse serum pig with a negative reaction on the test pig.

EFFECT OF TYPHOID VACCINE AND HORSE SERUM ON TESTS WITH DIPHTHERIA AND DIPHTHEROID ORGANISMS

The third series (Table 3) consists of pure cultures of virulent and nonvirulent diphtheria organisms and virulent and nonvirulent diphtheroid organisms. Each test includes four pigs in the series; a test pig, a control pig with antitoxin, a pig with typhoid vaccine, and a pig with horse serum.

TABLE 2.—Effect of Intracardial Injection of 1 c.c. Normal Horse Serum Immediately Preceding the Injection of B. Diphtheriae Intracutaneously, Compared with Test Pigs and Antitoxin Controls

Number and Strain of B. diphtheriae		Antitoxin Control Pig	Test Pig				Horse Serum Pig			
			First Reaction Noted	Necrosis	Lesion Cleared	Notes	First Reaction Noted	Necrosis	Lesion Cleared	Notes
51	40*	—	24 hours	— ?	Died in 48 hours	.....	72 hours	3d day	4 days	
52	44	—	24 hours	— ?	Died in 48 hours	.....	—	—	—	No reaction
53	45	—	14 hours	— ?	Died in 48 hours	.....	—	—	—	No reaction
54	50	—	14 hours	36 hours	Killed in 48 hours	.....	—	—	—	No reaction
55	52	—	14 hours	—	—	Negative	—	—	—	No reaction
56	53	—	14 hours	—	Killed in 48 hours	Negative	—	—	—	No reaction
57	55	—	—	—	—	Negative	—	—	—	No reaction
58	56	—	16 hours	16 hours	Died in 40 hours	Strongly positive	16 hours	40 hours	13 days	Slower development
59	57	—	16 hours	16 hours	Died in 36 hours	Very virulent	16 hours	5 days	9 days	Slow development of necrosis
60	61	—	16 hours	16 hours	.....	Very virulent	16 hours	40 hours	13 days	Slow development
61	68*	—	—	—	Died in 96 hours	Sub. q.	40 hours	5 days	9 days	
62	80	—	—	—	—	Negative	16 hours	5 days	19 days	Positive
63	65	—	16 hours	40 hours	Pig killed	.....	16 hours	72 hours	12 days	Slower development
64	88	—	16 hours	4th day	Pig died	.....	16 hours	72 hours	9 days	
65	89	—	—	—	—	Negative	—	—	—	No reaction
66	97	—	72 hours	72 hours	4 days	.....	—	—	—	No reaction
67	102	—	48 hours	72 hours	Pig killed	.....	—	—	—	No reaction
68	107	—	24 hours	48 hours	Died in 72 hours	Very virulent	24 hours	72 hours	23 days	
69	109	—	48 hours	48 hours	Died in 72 hours	Very virulent	24 hours	72 hours	6 days	
70	111	—	24 hours	72 hours	Died in 72 hours	.....	24 hours	72 hours	23 days	
71	114	—	24 hours	48 hours	Pig killed	.....	24 hours	—	4 days	
72	115	—	—	—	—	Negative	—	—	—	No reaction
73	140	—	—	—	—	Negative	—	—	—	No reaction
74	142	—	60 hours	72 hours	12 days	.....	—	—	—	No reaction
75	145	—	36 hours	36 hours	12 days	.....	—	—	—	No reaction

* Virulent on subcutaneous test. Twenty-five different strains tested on 42 pigs.

The findings, in general, are those of the first series—a more severe reaction which lasts longer with the typhoid pig showing a lowered resistance and a less marked reaction with the horse serum pig showing some protective action on the part of horse serum. Table 3 is also of interest because it shows a virulent diphtheroid, strain 82, in which there is a positive reaction on the antitoxin control pig as well as the test and nonspecific protein pigs. There is also another strain, No. 143, a diphtheroid by morphology and fermentation tests which on virulence tests acts as a true virulent diphtheria organism.

PROTECTIVE AND THERAPEUTIC EFFECT OF TYPHOID VACCINE AND HORSE SERUM ON SUBCUTANEOUS INJECTION OF DIPHTHERIA CULTURES

If there is a protective action in horse serum and a lowered resistance with typhoid vaccine it should show on the subcutaneous test with a known virulent strain of *B. diphtheria*. Strain 15, a granular type, fermenting dextrose and dextrin, which was isolated from a case of mild diphtheria Jan. 8, 1920, kills guinea-pigs in from thirty to seventy-two hours, when 1 c.c. suspension of a twenty-four hour growth is injected subcutaneously.

The first series consists of thirty pigs. These pigs are divided into groups of 2. Forty-eight hours preceding the time set for the subcutaneous injection of *B. diphtheriae,* one group is given 250 million dead typhoid organisms intracardial and another group 1 c.c. of normal horse serum; this is repeated with successive groups at intervals corresponding to twenty-four hours, six hours, two hours, one hour and one-half hour, and immediately preceding the injection of cultures of strain 15. Thirty pigs can be given subcutaneous injections within a time interval of twenty minutes. The suspension is made by pooling the twenty-four hour growth on thirty-five Loeffler tubes in 35 c.c. of sterile 0.9 per cent. sodium chlorid solution. One c.c. of this pooled suspension is injected into each pig. The test pigs received this suspension without other treatment. All pigs that die are autopsied. A subcutaneous virulence test is read as positive if a 1 c.c. suspension causes the death of a standard sized guinea pig in 120 hours.

The second series consists of thirty-two pigs all of which are given 1 c.c. of a pooled suspension of a twenty-four hour growth on thirty-five Loeffler tubes in 35 c.c. of sterile salt solution subcutaneously. The total time for all the subcutaneous injections is under twenty minutes. Immediately following the subcutaneous injection, one group of two pigs is given 250 million dead typhoid organisms, one group of two pigs (the test pigs) receive no other treatment and one group of two pigs is given 1 c.c. of normal horse serum intracardially. Typhoid and

TABLE 3.—Effect of Intracutaneous Injection of Virulent Diphtheria, Nonvirulent Diphtheria, Virulent Diphtheroids in Test Pigs, Control Pigs and Nonspecific Protein Pigs

Series No.	Culture No.	Control Pig	Test Pig			Typhoid Vaccine Pig			Horse Serum Pig		
			First + Reading	Necrosis	Lesion Cleared	First + Reading	Necrosis	Lesion Cleared	First + Reading	Necrosis	Lesion Cleared
100	43§	—	7 hours	3d day	Pig killed 3d day	18 hours	3d day	Pig died on 4th day	3d day	3d day	4 days
101	140§	—	60 hours	60 hours (3 mm.)	12 days	60 hours	60 hours (24 mm.)	Present in 28 days	60 hours	60 hours (4 mm.)	5 days
102	141§	—	—	—	—	Hyperemia 18 hours	—	24 hours	—	—	—
103	142§	—	60 hours	72 hours (2 mm.)	12 days	60 hours	5 days (5 mm.)	Present in 14 days	—	—	—
104	144§	—	—	—	—	60 hours	5 days	12 days	—	—	—
105	145	—	36 hours	36 hours (3 mm.)	12 days	60 hours	3 days (10 mm.)	Present in 14 days	—	—	—
106	143¶	—	72 hours	3d day (4 mm.)	12 days	—	—	—	—	—	—
107	139‡	—	—	—	—	—	—	—	—	—	—
108	134†	—	—	—	—	—	—	—	—	—	—
109	131*	—	—	—	—	—	—	—	—	—	—
110	82#	+	16 hours	72 hours	Pig died on 4th day	16 hours	40 hours	9 days	16 hours	40 hours	9 days

* Diphtheroid by morphology and fermentation tests.
† B. xerosis.
‡ From a case of pleuropneumonia in a child. By morphology, true diphtheria, by fermentation tests diphtheroid.
§ True granular diphtheria.
¶ Diphtheroid by morphology and fermentation test. Note virulence.
# B. diphtheroides liquefaciens.

horse serum injections are repeated at one-half, one, two, nineteen and twenty-four hours postinjection for both of the nonspecific proteins and three, four and six hours postinjection for the normal horse serum pigs.

Each series is controlled by two pigs receiving 250 units of antitoxin, and the 1 c.c. suspension of virulent diphtheria organisms subcutaneously. These pigs are not included in the charts. All these control pigs are living on the seventh day.

It is strikingly shown that all the pigs receiving an intracardial injection of typhoid vaccine and a virulent diphtheria organism subcutaneosuly die in less than 120 hours, regardless of whether the nonspecific protein is injected forty-eight hours before or twenty-four

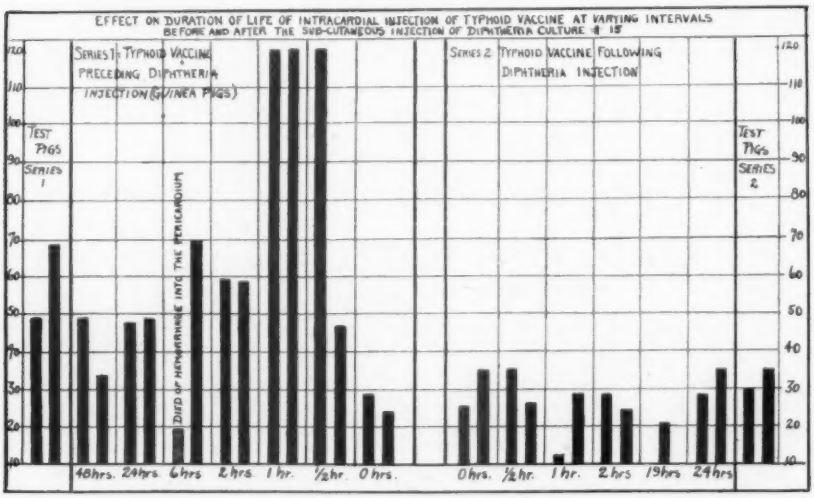
EFFECT ON DURATION OF LIFE OF INTRACARDIAL INJECTION OF TYPHOID VACCINE AT VARYING INTERVALS BEFORE AND AFTER THE SUB-CUTANEOUS INJECTION OF DIPHTHERIA CULTURE # 15
SERIES 1. TYPHOID VACCINE PRECEDING DIPHTHERIA INJECTION (GUINEA PIGS)
SERIES 2. TYPHOID VACCINE FOLLOWING DIPHTHERIA INJECTION
TEST PIGS SERIES 1
TEST PIGS SERIES 2
DIED OF HEMORRHAGE INTO THE PERICARDIUM
48hrs. 24hrs. 6hrs. 2hrs. 1hr. ½hr. 0hrs.
0hrs. ½hr. 1hr. 2hrs. 19hrs. 24hrs.

Fig. 1.—Black columns indicate dead guinea-pigs, the height of the column corresponding to the duration of life in hours.

hours afterward. The test pigs and twenty-two of the typhoid pigs are dead in less than seventy hours, while three pigs live 120 hours. There is evidently no protection given by typhoid vaccine against diphtheria inoculations in guinea-pigs. Typhoid vaccine has no therapeutic value in the treatment of diphtheria infections in guinea-pigs.

Normal horse serum, on the contrary, shows a very definite protective value given from forty-eight hours to immediately preceding the subcutaneous inoculation with *B. diphtheriae,* No. 15. Untreated pigs die in less than seventy hours, while twelve out of fourteen pigs given 1 c.c. of horse serum are living at the end of five days. Of the two that are dead, one died in eighteen hours following the intracardial injection due to hemorrhage into the pericardium. The other died in

fifty hours postinoculation, showing typical hemorrhage into the suprarenals, congestion of the lungs and fluid in both pleural and peritoneal cavities. Following the subcutaneous inoculations of guinea-pigs with virulent diphtheria organisms, 1 c.c. of horse serum will protect, if it is given any time up to five hours postinoculation. After six hours it has no effect, the pigs dying in the same period of time (under thirty-five hours) as the test pigs of this series.

Horse serum protection is in no way comparable in its protective value to the action of large doses of antitoxin. Cruveilhier [9] could rescue guinea-pigs sixteen hours after injection with a virulent diphtheria strain by the intravenous injection of antitoxin where untreated animals died in from thirty-six to forty-eight hours.

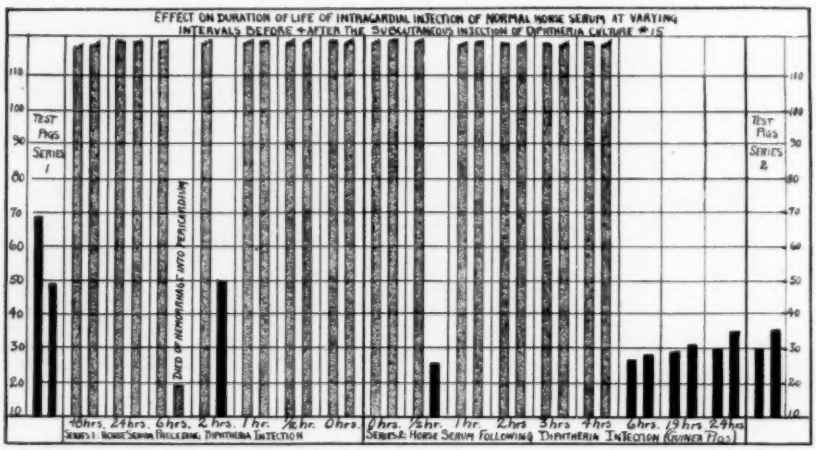
EFFECT ON DURATION OF LIFE OF INTRACARDIAL INJECTION OF NORMAL HORSE SERUM AT VARYING INTERVALS BEFORE & AFTER THE SUBCUTANEOUS INJECTION OF DIPHTHERIA CULTURE #15
TEST PIGS SERIES 1
DIED OF HEMORRHAGE INTO PERICARDIUM
TEST PIGS SERIES 2
48hrs. 24hrs. 6hrs. 2hrs. 1hr. ½hr. 0hrs.
SERIES 1: HORSE SERUM PRECEDING DIPHTHERIA INJECTION
0hrs. ½hr. 1hr. 2hrs 3hrs 4hrs 6hrs. 19hrs 24hrs
SERIES 2: HORSE SERUM FOLLOWING DIPHTHERIA INJECTION (GUINEA PIGS)

Fig. 2.—Black columns indicate dead guinea-pigs, the height of the column corresponding to the duration of the life in hours. Stippled columns indicate pigs living at the end of the period of observation.

Kolle and Schloszberger,[6] using diphtheria toxin, find that there is a certain death retarding effect but that it is slight, and it decreases with the time interval. With very small doses of antitoxin, the pigs died of necrosis after from twenty to twenty-five days. Of their 216 antitoxin treated pigs, 70 per cent. lived, while of 137 horse serum treated pigs, 80 per cent. died. They speak of the extensive necrosis which occurs with small doses of antitoxin. This necrosis occurs constantly in the horse serum tested pigs and is so extensive that the pigs are killed in from seven to fourteen days. Three pigs from the series illustrated in the charts are shown in Figure 3.

9. Cruveilhier, L.: De la Valeur Thérapeutique des injections de Serum dans la diphtherie suivant les doses et la voie de penetration, Ann. de l'Inst. Pasteur **18**:41, 1904.

The necrosis extends to the deeper muscle layers in the abdominal wall. In a few pigs showing a slighter degree of necrosis, the ulcer heals with smooth scar tissue, and no hair develops on the area of the scar.

FACTORS ENTERING INTO THE PROTECTIVE ACTION OF HORSE SERUM

What are the factors entering into this protective action of horse serum? Hektoen and Curtis [10] find that the injection of 1 c.c. of 10 per cent. suspension of rat blood per kilo of body weight in dogs produces specific opsonins and agglutinins which run parallel and only

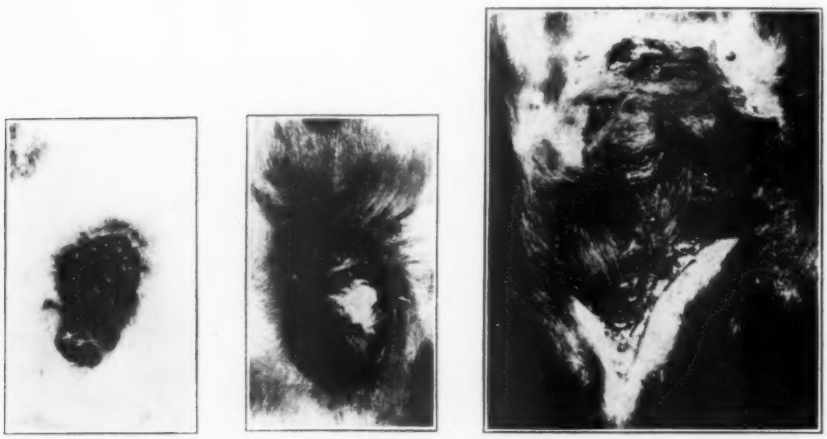

Fig. 3 a Fig. 3 b Fig. 3 c

Fig. 3.—Necrosis in horse serum treated pigs. Photographed by Johannes Andersen.

small amounts of lysin and precipitins are produced. Herrmann [11] believes that the intravenous injection of foreign protein serves as a stimulus for the liberation of specific antibodies in animals in which the previously injected antigen (streptococcus) is unable to cause such liberation. Jobling and Petersen [12] show marked change in the ferments and antiferments in the blood in protein shock, the protease and ereptase increase probably aiding in detoxication. They think toxins are hydrolyzed by ferments to lower nontoxic forms, so that a temporary improvement of a few days' duration may be observed, but that bacteria themselves are unaffected by these ferments. This latter may

10. Hektoen and Curtis: The Effect on Antibody production of the Removal of Various Organs, J. Infect. Dis. **17**:409, 1913.

11. Herrmann, S.: Liberation of Antibodies on the Injection of Foreign Proteins, J. Infect. Dis. **23**:457, 1918.

12. Jobling, J. W., and Petersen, W.: Bacteriotherapy in Typhoid Fever, J. A. M. A. **65**:515, 1915.

perhaps explain the question of the protection with horse serum injections, for the dose of 1 c.c. intracardially of horse serum is an enormous dose for a 250 gm. guinea-pig—roughly speaking it increases the guinea-pig's blood fluids by one-eighth of the total blood volume, and the simple injection of that quantity of antibodies may give protection until the body is able to mobilize its own protective forces. Or, perhaps, protection may be the result of nonspecific protein reactions. This, at first glance, seems untenable since typhoid vaccine gives no protection in guinea-pigs. But what constitutes the nonspecific protein reaction? The phenomenon of protein shock is characterized by the syndrome of chills, fever and changes in the blood picture during the first forty-eight to seventy-two hours after intravenous injection of a foreign protein.[13]

In guinea-pigs it is difficult to measure the temperature response to a specific agent since fright and excitement without any other factors will cause change of as much as 3 degrees in the rectal temperature of a guinea-pig, and an animal unaccustomed to handling will frequently shake as though with a chill when it is handled. No definite physical symptoms are noted after intracardial injection of 0.25 c.c. of typhoid vaccine. Increasing the volume up to 1 c.c. by diluting with normal salt also has no effect on the physical reaction. The horse serum pigs, however, exhibit some respiratory distress immediately following the injection of 1 c.c. To check the existence of protein shock blood counts are made following the method used by Cowie and Calhoun [15] in studying the effect of nonspecific protein therapy in arthritis. Leukocyte counts are made preceding the injection of the typhoid vaccine and horse serum, every half hour postinjection for two hours, and then every hour until the count returns to normal. The blood is taken from the ear of the guinea-pig, diluted with 1 per cent. acetic acid in the white pipet and counted in a Levi chamber. Both pipet and counting chamber have been tested and certified by the U. S. Bureau of Standards. The normal picture of a foreign protein reaction is a leukopenia followed by a leukocytosis chiefly due to an increase in the polymorphonuclear group. In man there are two types of the reaction; one with a prompt rise from the leukopenia, followed by a

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* Barach [14] criticizes the statement made by Cowie and Calhoun,[15] that the protein shock or nonspecific protein reaction is not anaphylactic in its nature. We hold that there is a clear distinction between the primary protein shock reaction, and the secondary anaphylactic response to a previous sensitization—anaphylaxis meaning always a reaction to a preceding injection which is specific for the protein injected.

13. Borach [14] criticizes the statement made by Cowie and Calhoun,[15] that the

14. Barach, J. H.: Leukocytes in Anaphylaxis of Serum Sickness, J. Lab. & Clin. M. **5**:295 (Aug. 7) 1920.

15. Cowie and Calhoun: Nonspecific Therapy in Arthritis and Infections, Arch. Int. Med. **23**:60 (Jan.) 1919.

permanent return to normal in from nine to twelve hours; and the other, the type with a primary rise and fall which is followed in the course of from six to twenty-four hours by a secondary rise, sometimes to a higher point than the first—the pendulum type described by Miller and Lusk.[16]

ESTABLISHMENT OF NORMAL WHITE BLOOD COUNT IN GUINEA-PIGS

Eyre [17] gives the normal white count for a guinea-pig as 10,000 per c.mm. This is found to be subject to wide variation in different pigs, and in the same animal at different times of the day.

Counts made on three normal pigs at two hour intervals, seven counts in each series, show a range of from 6,200 to 14,300 leukocytes, with the peak count between 2 and 3 p. m. Counts made on twenty-four different pigs between 8 and 10 a. m. show a leukocyte range of from 6,400 to 21,500, distributed as follows:

TABLE 4.—LEUKOCYTE COUNT MADE BETWEEN 8 AND 10 A. M.

Number of Pigs	Leukocyte Range
1	21,500
13	10,500-15,000
6	9,500-10,500
3	8,000- 9,500
1	6,400

From these figures it seems that the normal range of the leukocyte count in healthy standard size guinea-pigs is from 8,000 to 15,000. Guinea-pigs showing an initial count falling outside this range were not used for the study of the blood reactions.

For purposes of facilitating comparison, the counts on individual pigs are reduced to the standard average of 10,000 for the initial count and the curves are calculated on the basis of percentage of increase or decrease from the true initial count. The individual normal range is between 8,000 and 15,000, the counts in normal pigs tending to remain in most cases above the 10,000 line rather than below it.

LEUKOCYTE COUNT AFTER INJECTION OF TYPHOID VACCINE AND HORSE SERUM

The effect on the leukocyte count of the intracardial injection of 250 million dead typhoid bacilli on two guinea-pigs is shown in Figure 4, the counts extending over a period of twenty-eight hours with a final count in thirty-six hours. This shows the startling fact that in guinea-pigs, 250 million dead typhoid organisms do not give the typical blood picture of a foreign protein. For the first six to eight hours

16. Miller, J. L., and Lusk, F. B.: The Treatment of Arthritis by the Intravenous Injection of Foreign Proteins, J. A. M. A. **66**:1756 (June 3) 1916.

17. Eyre, J. W. H.: The Elements of Bacteriologic Technic, Ed. 2. Philadelphia, W. B. Saunders & Company, 1915, p. 374.

there is a tendency for the count to drop below the normal limits and a definite leukocytosis does not occur before from twenty-three to twenty-six hours postinjection. Its range is from 23,000 to 26,000 per c. mm. From this we must conclude that foreign proteins do not act as foreign proteins for all animals—either the guinea-pig does not have the ability to split the protein of the typhoid organism, or, on being split, typhoid protein does not liberate harmful or stimulative substances that are able to act on the spleen, bone marrow and lymphatic centers—the mesenchymal fundaments. That the action of non-

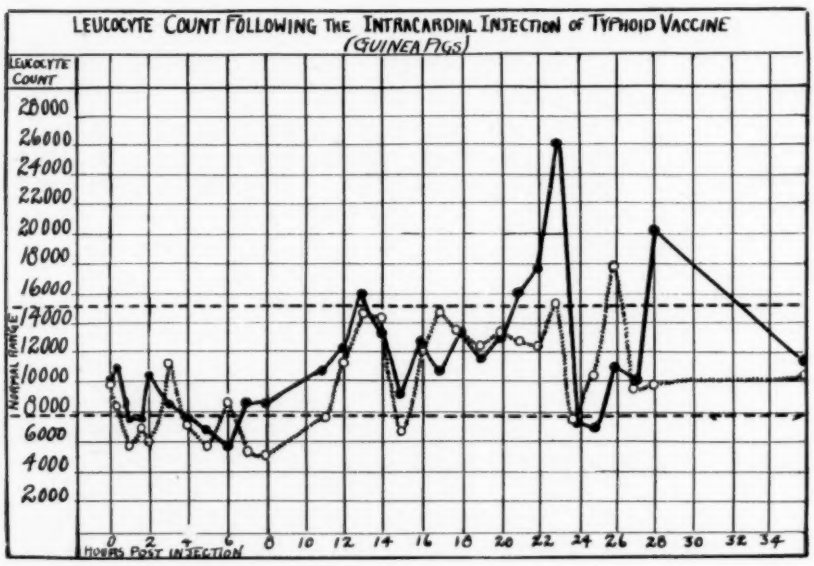

Fig. 4.—Individual counts on two guinea-pigs shown by solid and dotted lines.

specific proteins varies in different species of animals is also borne out by the fact that Cohen [18] finds that parenteral injection of egg white has no effect on the temperature of the dog, although the egg white is absorbed from the point of injection and is not excreted in the urine as egg white, but in the guinea-pig the injection of egg white produces the typical protein fever.

The leukocyte count following the intracardial injection of 1 c.c. of normal horse serum shows the typical foreign protein curve. The two pigs illustrated show the two types of curves, one the simple leukopenia and hyperleukocytosis and the other the leukopenia and a leukocytosis with a pendulum swing, the second rise being the highest, with a third rise in thirty-six hours. There is no doubt that here there is a definite foreign protein blood picture which seems to add evidence

18. Cohen, S. J.: Protein Fever: the Effect of Egg White Injection on the Dog, J. Lab. & Clin. M. **5**:285, 1920.

to the theory that the cellular elements play an essential part in the protective mechanism of the body. The increase in leukocytes appears even more marked when the volume dilution of one-eighteenth is recalled.

What is the relationship between the leukocyte change in diphtheria intoxications and the time interval beyond which the horse serum exerts no protective or therapeutic value? Figure 6 shows the counts made on two pigs which received a subcutaneous injection of a 1 c.c. suspension of a twenty-four hour growth on Loeffler's blood serum of *B. diphtheriae* strain 15.

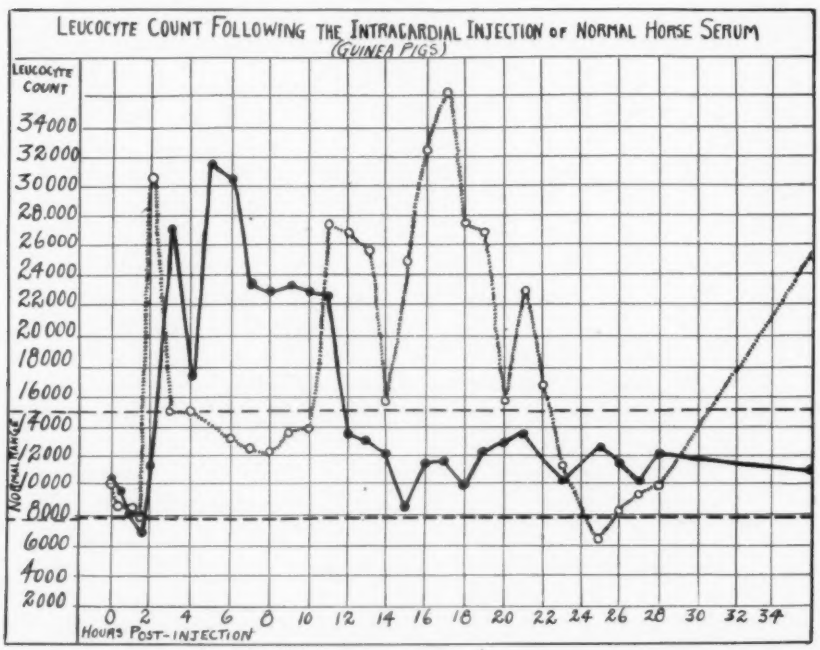

Fig. 5.—Individual counts on two guinea-pigs shown by solid and dotted lines.

There is a leukocytosis which reaches its first peak in from four to ten hours and is followed by a fall, with a second marked rise in twenty-two hours and a rapid fall preceding death. One pig shows a maximum leukocytosis of 68,000, the other a maximum of 30,000. With an injection of horse serum up to six hours postdiphtheria injection it may be noted that the leukopenia stage occurs with a rising count in the untreated pig and the first leukocyte rise in the horse serum pig with a falling leukocyte count in the diphtheria pig. However, it is impossible to get any definite correlation on counts following the simultaneous injection of the typhoid vaccine and the organism, the curves in different pigs showing wide variations.

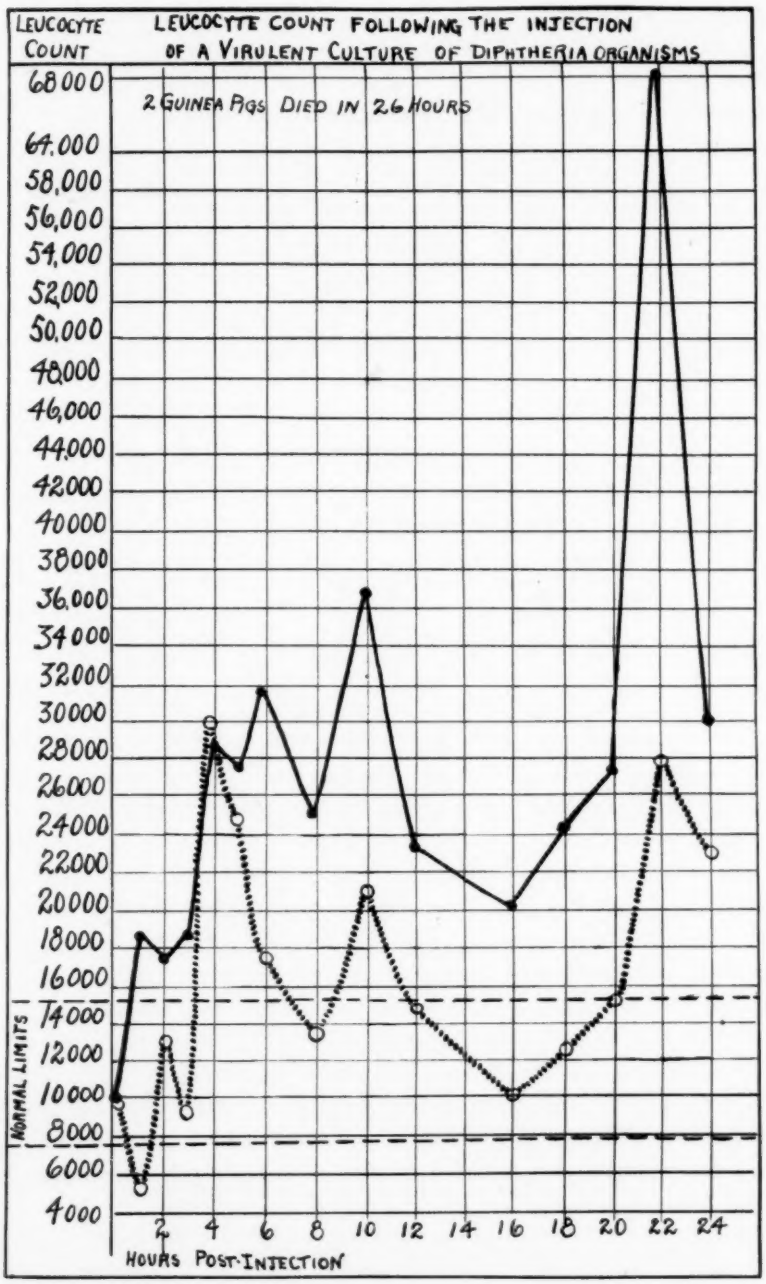

Fig. 6.—Individual counts on two guinea-pigs shown by solid and dotted lines.

Counts made on pigs receiving 0.25 c.c. of horse serum volume containing 250 units of antitoxin do not show any definite variations from the normal.

TESTS OF ANTITOXIN EQUIVALENT OF HORSE SERUM

Is there a possibility that horse serum may derive its protective action from its antitoxic content? Many horses produce low titers of antitoxin and many undoubtedly naturally produce serums with small amounts of antitoxin. Diphtheria toxin (Mulfords No. 837.5) was obtained. The L + dose is 0.20 c.c. If 0.20 c.c. of the toxin will just kill a standard sized guinea-pig which has been given 1 unit of antitoxin in 5 days then it is possible to ascertain the antitoxin equivalent of the 1 c.c. horse serum used.

TABLE 5.—TEST FOR ANTITOXIN CONTENT OF HORSE SERUM

Number of Pigs	Amount of Toxin, C.c.	Amount of Horse Serum, C.c.	Results
2	0.20	0	Death in 18 hours
2	0.20	0.25	Death in 24 hours
2	0.20	0.35	Death in 100 to 120 hours
2	0.20	0.50	Living in 7 days
1	0.20	1.0	Living in 7 days
2	0.20	1 standard unit antitoxin	Death in 100 to 118 hours

This shows that there is less than one unit value of antitoxin in 0.33 c.c. horse serum used since the pigs with an L + dose are not protected for five days, while 0.5 c.c. horse serum contains more than one unit value of antitoxin. Consequently, the antitoxin equivalent of 1 c.c. horse serum is between 2 and 3 standard units of antitoxin. Of course, this does not rule out the possibility that the antitoxin equivalent of horse serum may be due to some other antibodies, opsonins, agglutinins,[10] and ferments or antiferments as protease or ereptase [12] which may be present in the horse serum injected, in sufficient quantity to protect; or to antibodies which may be developed in the blood of the guinea-pig as a result of the foreign protein reaction to horse serum. This point cannot be settled by animal experimentation until we have a new method for testing antitoxin. Personally, I think the antibody is probably specific diphtheria antitoxin contained in the horse serum.

PROTECTIVE VALUE OF SMALL AMOUNTS OF ANTITOXIN

Can the small amount of antitoxin in 1 c.c. horse serum protect a 250 gm. guinea-pig for five days against a subcutaneous injection of a virulent strain of *B. diphtheriae*?

To determine this a series of twenty-five pigs are inoculated. Four are used as test pigs, and three of each set are given a varying amount of standard measurable units of antitoxin. This antitoxin is from the hygienic laboratory and was obtained through the kindness of Dr. McCoy. In doses of from 12 to 24 units it is necessary, because of the dilution, to inject the antitoxin subcutaneously. The remaining tests are all intracardial.

The diphtheria organism selected is strain 198, which kills test pigs in from eighteen to forty hours after the subcutaneous injection of 1 c.c. suspension of a twenty-four hour growth on Loeffler's tubes. The growth on thirty-five tubes is pooled in 35 c.c. of sterile isotonic salt solution, and each pig is given 1 c.c. of this suspension. One unit of antitoxin retards death, from one and one-half to six days; 3 units of antitoxin retard death from seven to eight days, and 6 units and

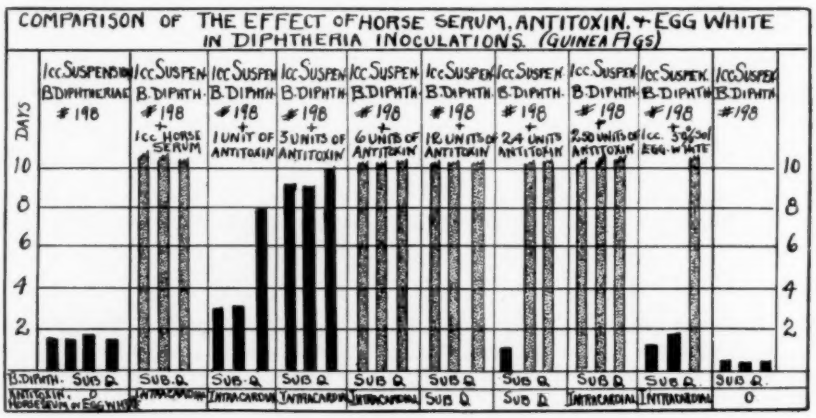

Fig. 7.—Black columns indicate dead guinea-pigs, the height of the column corresponding to the duration of life in hours. Stippled columns indicate pigs living at the end of the period of observation.

over (with one exception) protect against virulent diphtheria organisms. The most interesting fact is that, although 1 c.c. horse serum contains an antitoxin equivalent of less than three units, the smallest dosage of a standard antitoxin that will give the same protection is 6 units.

PROTECTIVE FACTORS IN HORSE SERUM

This seems to show that the big factor in horse serum protection against virulent diphtheria organisms in guinea-pigs is its antitoxin equivalent, and yet that this is not the only factor is shown by the fact that the equivalent amount of antitoxin does not give as efficient protection. Is this additional factor the nonspecific protein reaction?

The tests with typhoid vaccine do not give any clue to this because in a guinea-pig the dead typhoid bacilli do not give the protein response. To check this point a series of six pigs—three test pigs and three protein pigs—are used for tests with egg white, which gives a protein reaction in guinea-pigs. The dosage of egg white is 1 c.c. of a 50 per cent. solution of egg white in sterile salt solution, injected into the heart. The results are also shown in Chart 7. The egg white pigs lived from twenty-four hours to 14 + days longer than the corresponding test pigs. This means that there is a retardation of the time of death caused by the injection of egg white, which in one case out of three was equivalent to that produced by horse serum or by 6 units of antitoxin. The foreign protein reaction on the part of the guinea-pig following the injection of horse serum must be considered as a part of the protective power of the horse serum.

It must be concluded that the mechanism of this protective power is due: first, to an antibody, probably antitoxin in the horse serum; and second, to the calling forth of the protective forces in the guinea-pig, chiefly, I believe, in the form of cellular response to the foreign proteins in the horse serum that aids in the protection. Undoubtedly, the antitoxin factor is the most important because there is cellular response called forth by the subcutaneous inoculation with living diphtheria cultures, the leukocyte counts made at intervals on test pigs following the inoculation showing the pendulum type of curve. The diphtheria curves do not exactly coincide with the foreign protein curves in the time of development, but this may be due to the fact that the typhoid vaccine, egg white and horse serum are given intracardially in the form of protein, and the diphtheria organisms are given intracutaneously in the form of living protoplasm which may give no reaction until it is autolyzed.

The controversy over the question of the relative importance of the value of cellular response and of the soluble antibody production as a result of the injection of a foreign protein is still unsettled. However, I cannot help but feel that this adds corroborative evidence to the findings previously given by Cowie and Calhoun, that in arthritis the most marked and permanent improvement in protein treated cases occurs in those cases in which there is the most marked cellular response, a response that calls forth both the reserve and the unfinished blood cells and is evidenced by the appearance of myelocytes and nucleated red cells.

CONCLUSIONS

1. Typhoid vaccine, administered intracardially, increases the sensitiveness of the virulence tests both by the intradermal and the subcutaneous methods. With intradermal injection the reaction is earlier,

more marked and persists for a longer period of time, and the percentage of positives is larger than in ordinary test pigs.

2. Horse serum injected intracardially decreases and inhibits the intracutaneous test for virulent diphtheria organisms. In guinea-pigs injected with horse serum inoculations showing a positive reaction on intracutaneous tests the lesions are less marked and clear up more rapidly than in the corresponding test pigs.

3. Organisms whose morphology, and fermentation tests are those of diphtheroids may show positive virulence tests either with or without protection by antitoxin and may give the same reactions with typhoid vaccine and with horse serum as virulent diphtheria organisms.

4. On subcutaneous inoculations of virulent cultures of *B. diphtheriae,* typhoid vaccine does not prevent the death of the guinea-pig nor alter the course of the disease when injected either before or after the inoculation.

5. Horse serum injections (1 c.c. intracardially) given forty-eight hours to immediately preceding the subcutaneous diphtheria inoculation, prevent the death of standard size guinea-pigs, although there is no protection from the development of extensive necrosis at the site of the inoculation in from one to three weeks. Horse serum injections (1 c.c. intracardially) will protect a standard sized guinea-pig if given within five hours after the diphtheria inoculation. After five hours it has no curative or protective value.

6. Horse serum and typhoid vaccine are not interchangeable foreign proteins for guinea-pigs. Typhoid vaccine offers no protection and horse serum has a distinct protective reaction.

7. Study of the leukocyte reactions following the injection of typhoid vaccine in guinea-pigs does not show the typical foreign protein reaction, while horse serum injection gives the typical leukopenia and leukocytosis of both the simple single reaction and the pendulum types found in man. Typhoid protein has not called forth the nonspecific protein response in guinea-pigs. It is of importance in experimental studies in animals of foreign proteins to determine the ability of the species to split the protein to be tested. Antitoxin in 0.25 c.c. volume of horse serum does not cause a similar leukocytosis.

8. Diphtheria inoculation subcutaneously causes a marked leukocytosis and a pendulum swing not unlike that of foreign proteins.

9. Normal horse serum contains a variable number of antitoxin units. The specimen used contains less than 3 units per c.c., and undoubtedly the protective value of horse serum in these experiments is due for the greatest part to the antitoxin content. Yet it is impossible to rule out the probability that in addition there is another factor, which may be that of a nonspecific protein reaction, since egg white

increases the length of life or in isolated cases protects guinea-pigs against virulent diphtheria organisms.

10. The question of the importance of cellular response in nonspecific protein therapy is still unsettled. These experiments showing no protection in guinea-pigs by typhoid vaccine which does not give a cellular response, and the protection given by egg white which produces a definite leukocytosis, strengthen the previously stated view of Cowie and Calhoun that the therapeutic results of nonspecific protein in arthritis depend on the stimulation of the mesenchymal fundaments for blood cell production.

11. There is experimentally no sufficient basis for substituting nonspecific protein for the specific antiserum treatment of diphtheria infections and intoxications. Antitoxin in the usual dosage is more efficient in every way than horse serum, and should be used by preference when procurable. In extraordinary situations where antitoxin absolutely cannot be obtained horse serum in large doses should be used as a substitute.

12. Even as small amounts of antitoxin as 6 units will protect a 250 gm. guinea-pig against the injection of virulent diphtheria organisms and the value of diphtheria antitoxin in diphtheria is emphasized by the results of these experiments.

I want to acknowledge my indebtedness to Dr. Henry Albert for constant encouragement and helpful suggestions, and to the Committee on Scientific Research of the American Medical Association for their financial assistance.

SOME EXPERIMENTS TO DETERMINE THE PERSISTENCE OF EXTRANEOUS BACTERIA IN THE GASTRO-INTESTINAL TRACT OF GUINEA-PIGS AS INFLUENCED BY DIET*

A. GRAEME MITCHELL, M.D., AND PAUL LEWIS, M.D.

PHILADELPHIA

INTRODUCTION

It is commonly believed that the character of the bacterial flora of the gastro-intestinal tract has an important influence on health. In certain instances this is unquestioned. The implantation of sufficient numbers of certain bacteria, *B. typhosus, B. dysenteriae* or *Vibrion cholerae* in the absence of a counteracting general bodily immunity brings about the development of the infections specifically related to these organisms. So also, but possibly in a less specific way, the less well characterized gastro-intestinal disturbances of infancy and childhood are commonly supposed to be due either to the activity of particular species of bacteria or to an alteration in prevailing types of micro-organisms.

A relationship between the general type of bacterial flora prevailing in the gastro-intestinal tract and more obscure disorders, such as anemias and ill defined general intoxications, is often surmised, but scientific evidence of such an association cannot be said to have been presented convincingly. None the less, the administration of acid producing types of bacteria with the conception that they will be of benefit in limiting the activity of putrefactive types is widely practiced. A review of the literature leaves it a matter of great doubt whether the administration of the acid producing types leads to more than a most temporary change in the intestinal flora. The experiments of unbiased observers make it probable that after a short period the extraneous bacteria are completely eliminated. Assuming that the prevalence of a type of micro-organism or of a particular species is of favorable significance for the host, it becomes a matter of considerable interest to know on what condition or circumstance the survival of the favored type is possible.

This question is closely related to another of the same general character and of equal importance, namely, the periodic variation in the prevailing type of bacteria in the respiratory tract. Not that the

* Received for publication July 2, 1920.

* From the laboratory of the Henry Phipps Institute of the University of Pennsylvania, and the Medical Service of the Children's Hospital of Philadelphia.

* Read at the meeting of the American Pediatric Society, Highland Park, Ill., June 1, 1920.

causes of variation in the respiratory tract are likely to be identical with those in the intestine, but the principles on which these variations take place are likely to have important common features.

The problems involved are of great interest from a biologic point of view. A complete solution of them would doubtless influence practice. What our work has to offer, however, is not a solution—merely a beginning—and a suggestion as to a method of study not previously employed. The work here presented is in a sense an extension of experiments carried out some years ago by one of us (Lewis, unpublished) in the course of which the method of study was used and some of its limitations defined. Aside from outlining a method and the conditions met with as preliminary to experimentation in this field our present paper offers one point which seems to have real interest, namely, that while *B. pyocyaneus* quickly disappears from the normal gastro-intestinal tract on a normal diet, and does not persist longer when certain obviously unfavorable diets are offered, the addition of certain favorable factors (greens) to an otherwise unsatisfactory diet does tend to favor the persistence of this organism. This may warrant the suggestion that the relationships between particular bacterial species as persistent inhabitants of the intestinal tract and particular articles of diet may be closer than has hitherto been postulated, and this idea may be worthy of further study.

REVIEW OF LITERATURE

The intestinal flora of man and other animals has been studied extensively, and has been of especial interest to the pediatrist. Not only have the types of bacteria been investigated in various intestinal disorders, but the "switching" from a predominance of one type to another has been demonstrated.[1] Briefly stated, an excess of carbo-

1. Hull, T. G., and Rettger, L. F.: Further Studies on the Influence of a Lactose-Containing Diet on the Intestinal Flora, J. Bacteriol. **1**:120, 1916. Penrose, C. A.: A Review of the Theories and Facts Underlying the Treatment of Diseases by Soured Milk Cultures, Maryland M. J. **58**:53, 1915. Torrey, J. C.: The Regulation of the Intestinal Flora of Dogs Through Diet, J. Med. Res. **39**:415, 1919. Herter, C. A., and Kendall, A. I.: The Influence of Dietary Alterations on the Types of Intestinal Flora, J. Biol. Chem. **7**:203, 1910. Hull, T. G., and Rettger, L. F.: The Influence of Milk and Carbohydrate Feeding on the Character of the Intestinal Flora. IV. Diet Versus Bacterial Implantation, J. Bacteriol. **2**:47, 1917. Herter, C. A.: Experimental Variation of Intestinal Flora by Changes in Diet, Internat. Beitr. z. Path. u. Ther. der Ernährungsstörungen **1**:275, 1909. Herter, C. A.: The Common Bacterial Infections of the Digestive Tract and the Intoxications Arising from Them, New York, The Macmillan Co., 1907. Porter, L.; Morris, G. B., and Meyer, K. F.: Certain Nutritional Disorders of Children Associated with a Putrefactive Intestinal Flora, Am. J. Dis. Child. **18**:254 (Sept.) 1919. Distaso, A., and Sugden, J. H.: Entero-Intoxication—Its Causes and Treatment, Biochem. J. **13**:153, 1919. Ford, W. W.; Blackfan, K. D., and Batchelor, M. B.: Some Observations on Intestinal Bacteria in Children, Am. J. Dis. Child. **14**:354 (Sept.) 1917.

hydrate in the diet tends to favor the growth of the acid forming type of bacteria in the intestinal tract, while an excess of protein favors the growth of putrefactive organisms.

Some of Metchnikoff's pupils and followers have published investigations that attempt to support his hypothesis that the lactic acid bacillus is implanted in the digestive tract. Cohendy [2] concluded from the study of four human subjects that the *B. bulgaricus* appeared in the stool from three to five days after the first ingestion of that organism. It was found each day thereafter, and it was still present in the stool from twelve to twenty-four days after the last ingestion. In one of these patients it was revealed by an abdominal operation, which occurred during the course of the experiment, that the *B. bulgaricus* multiplied in the upper two-thirds of the colon. Results similar to these were obtained by Leva.[3] Later Cohendy experimented with thirty other subjects, including himself. In this later work he apparently did not attempt to recover the ingested organism from the stool.

Belonovsky [4] conducted experiments on mice over a period of ten months. After feeding the bulgarian ferment daily to these animals, he recovered the organism in ten days by culturing the stool, and found that it persisted in the intestinal discharges for about four weeks after the return to a normal régime and the cessation of germ feeding. The author states that on examining the excrement under the microscope, there was no predominance of the bulgarian bacillus. Control mice were fed various substances, such as lactic acid, sterilized milk, bulgarian ferment killed by heat, and other organisms (*B. pyocyaneus* and *B. prodigiosus*). It was only in mice fed with *B. bulgaricus* that the total number of bacteria in the droppings was diminished. It was apparently on such evidence as this that Metchnikoff based his claim of intestinal implantation of the bulgarian bacillus, as he himself does not seem ever to have demonstrated such a phenomenon.[5]

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2. Cohendy, M.: Essais d'acclimatation Microbienne Persistante dans la Cavité Intestinale. Delimitation du Siége Probable de cette Acclimatation, Compt. rend. Soc. Biol. **60**:364, 1906. De la Disinfection Intestinale Obtenue sans Régime Special par l'acclimatation d'un Ferment Lactique dans le Gros Intestin, Compt. rend. Soc. Biol. **60**:602, 1906.

3. Leva, J.: Zur Beurteilung der Wirkung des Lactobacillus und der Yoghurtmilch, Berl. klin. Wchnschr. **45**:922, 1908.

4. Belonovsky, J.: Influence du Ferment Lactique sur la Flore des Excrements des Souris, Ann. Inst. Pasteur **21**:991, 1907.

5. Metchnikoff, E., et al.: Bacteriotherapie, Vaccination, Serotherapie, J. B. Bailliere et Fils, Paris, 1909. Metchnikoff, E.: The Prolongation of Life, New York, Putnam Sons, 1908. Etudes sur la Flore Intestinale. Ann. Inst. Pasteur **27**:894, 1913. We are not concerned here with the question as to whether or not the feeding of the bacillus does good clinically. The subject under discussion is only that of the implantation of organisms in the intestinal tract.

The work of later investigators does not substantiate the theory of implantation.[6] Hull and Rettger performed one hundred and eighty individual experiments on white rats, six on other laboratory animals, and four on man. They collected and cultured the feces, but were unable to establish the *B. bulgaricus* in the intestinal tract, in spite of the ingestion of large numbers of these organisms. Herter and Kendall found that the exclusive feeding of a rhesus monkey for two weeks with milk fermented with the bulgarian bacillus failed to establish the predominance of this organism in the cecal region or in the colon. The experiments of Rahe show that the bacillus bulgaricus is capable of an apparently limited survival in the upper intestine of the monkey. Rahe's results are shown in Table 1.

TABLE 1.—RESULTS OF FEEDING B. BULGARICUS TO MONKEY

Monkey	Fed	Period of Ingestion	Time Killed after Last Ingestion	Duodenum	Jejunum	Ileum	Cecum	Feces
1	50 tablets per day.....	13 days	24 hours	—	+	—	—	—
2	300 c.c. 48-hr. milk culture.	6 days	7 hours	+	+	+	+	+
3	300 c.c. 48-hr. milk culture.	6 days	7 hours	+	—	—	—	—

More recently the *B. acidophilus,* a normal inhabitant of the intestinal tract of man, has been introduced by mouth in order to prevent the proliferation of the proteolytic types of organisms. It may be said, however, that the proof of the implantation of organisms in the intestinal tract of man or of laboratory animals rests on incomplete evidence.

METHOD OF PROCEDURE

We have approached this subject from a somewhat different angle than previous investigators. The present study is concerned only with the attempt at implantation of an extraneous organism, the *B. pyocyaneus,* in the digestive tract of the guinea-pig. Our aim has been to study the principles governing the implantation, if such can be accomplished. If implantation should not be found possible, we may hope to find out the reasons back of this local immunity. *B. pyocyaneus* has several advantageous characteristics for a study of this kind: it is potentially pathogenic; it produces poisonous substances

6. Rahe, A. H.: A Study of the So-Called Implantation of the Bacillus Bulgaricus, J. Infect. Dis. **16**:210, 1915. Editorial, J. A. M. A. **73**:1844 (Dec. 13) 1919. Herter, C. A., and Kendall, A. I.: An Observation on the Fate of Bacillus Bulgaricus (in Bacillac) in the Digestive Tract of a Monkey, J. Biol. Chem. **5**:293, 1908. Luerssen, A., and Kuhn, M.: Yoghurt, die Bulgarische Saurmilch, Centralbl. f. Bakteriol. **20**:234, 1908 (Quoted by Hull and Rettger, J. Bacteriol. **2**:47, 1917. Heinemann, P. G.: Lactic Acid as an Agent to Reduce Intestinal Putrefaction, J. A. M. A. **52**:373, 1909.

in culture which in its pathogenic relationships it assumes in various character, and above all it is easy of recognition.

The guinea-pig has a comparatively sterile gastro-intestinal tract. This may readily be proved by killing a guinea-pig after a twenty-four hours' fast and taking smears and cultures from the various parts of the intestinal segments. One usually finds a moderate number of organisms in the smear from the stomach; often none from the duodenal smear; a rather large number from the ileum, cecum and colon. Cultures made on agar will frequently show no growth. This negative finding is especially constant in the duodenum. Such a distribution of bacteria corresponds to that found in the intestinal tract of man.[7] If the pig has not been in a state of fast and has a gastro-intestinal tract full of food, organisms found by smear and culture are more numerous, and different molds introduced with the food may grow in the culture. Again, if some time has elapsed between death and the taking of the smears and cultures, the organisms will be correspondingly numerous. The organisms found are gram-positive and gram-negative diplococci and bacilli, the types varying with the diet. (Cultures taken in the manner described show, of course, only the aerobic bacteria). It is possible for certain animals to live with sterile digestive tracts.[8]

The *B. pyocyaneus,* as far as we have been able to ascertain, is not a normal inhabitant of the gastro-intestinal tract of the guinea-pig. Furthermore, this organism has a low pathogenicity, for the guinea-pig can be fed in large numbers mixed with the food without causing ill effects. If fed in the manner as described it seldom enters the blood stream and causes a septicemia. It may, however, gain entrance to the circulation through the intestinal tract.[9] The *B. pyocyaneus* occasionally occurs in the digestive tract of the human apparently in the best of health. In some of our earlier experiments we introduced the *B. pyocyaneus* into the stomach of the guinea-pig by means of a small catheter used as a stomach tube. When a considerable number of organisms were introduced in this manner, the animal died exhibiting a violent gastro-enteritis and a growth of the bacillus was obtained

7. Contributions to the Science of Medicine by the Pupils of William Welch, 1900, p. 543, Cushing and Livingood.

8. Nuttall, G. H. F., and Thierfelder, H.: Thierisches Leben ohne Bakterien im Verdauungskanal, Ztschr. f. Physiol. Chem. **21**:109, 1895; **22**:62, 1896; **23**:231, 1897. Wolmann, E.: Sur l'elevage des Mouches Steriles, Ann. Inst. Pasteur **25**:79, 1911. Cohendy, M.: Experiences sur la Vie sans Microbe, Ann. Inst. Pasteur **26**:106, 1912. Bakteriologische Darmuntersuchungen, Skand. Arch. f. Physiol. **16**:249, 1904. Freeman, L.: Chronic General Infection with Bacillus Pyocyaneus, Tr. Am. Surg. Assn. **34**:113, 1916.

9. Freeman, L.: Chronic General Infection with the *Bacillus Pyocyaneus,* Tr. Am. Surg. A. **34**:113, 1916.

from the heart blood. If, however, no *B. pyocyaneus* could be recovered from the gastro-intestinal canal, no evidence of gastro-enteritis was observed when the animal was killed, and the culture from the heart was negative. This method was given up, for the time being at least.

TECHNIC

With the exception of these experiments the technic of the study was as follows: Guinea-pigs that were offered various diets were fed the *B. pyocyaneus* for variable lengths of time. Later, in order to make the experiments uniform, all the pigs were fed the germ for three days. A fresh twenty-four hour culture of a strain of the *B. pyocyaneus* which produced a brilliant green color was washed from an agar slant with about 5 c.c. of physiologic sodium chlorid solution and thoroughly mixed with the day's supply of food for the pig. On cessation of the feeding of *B. pyocyaneus,* nourishment of the pig continued with the various diets unmixed with the organism. At variable lengths of time the pigs were killed and cultures made on agar from the heart blood, the stomach, the duodenum, the ileum, the cecum and the colon. If the pig died the same cultures were made. These cultures were incubated for twenty-four hours, and after that kept at room temperature. No tube was declared negative for the *B. pyocyaneus* until at least five days had elapsed without evidence of green pigmentation. After having first ascertained that it was the *B. pyocyaneus* with which we were working, an appearance of the green pigment was considered sufficient evidence of the presence of that organism in the cultures. The + marks in the charts indicate the amount of green pigmentation appearing in the agar, + a small amount of the color; ++ a larger amount, coloring about half the agar slant; +++ when all the agar was permeated with the pigment.

A series of experiments was first undertaken to ascertain whether or not the *B. pyocyaneus* would grow in the gastro-intestinal tract of the guinea-pig, and whether or not diet had any effect on such growth. Previous to the feeding of the *B. pyocyaneus* mixed with the food, the pigs had been fed on their regular diet which consisted of oats and bread mixed with water, hay, and green stuff twice a week. Of the fourteen pigs used, three were continued on their regular diet and the *B. pyocyaneus* was mixed with the oats, bread and water for two days. *Bacillus pyocyaneus* was recovered from the cecum of two of these pigs when killed one or two days later, but not from the pig killed four days later. The remaining pigs in this series were kept on their regular diets until the day on which they received their first *B. pyocyaneus* feeding mixed with their new diets. They did not take the abnormal diet well, and there is, therefore, some doubt

as to the amount of germ ingested. However, in three of these pigs the *B. pyocyaneus* was recovered either from the ileum or cecum or both, when killed two days after having been previously fed *B. pyocyaneus* for two days. These three pigs had been fed on hay and water, milk and water, and crackers and water respectively. Other pigs in this series had been nourished on crackers and milk, bread and milk, bread and water, oats and water. From the pigs thus fed *B. pyocyaneus* could not be recovered when they were killed two days after the cessation of a two day period during which that organism had been administered with the food.

In order to find out whether the length of time during which the *B. pyocyaneus* was fed had any effect on its persistence in the digestive tract, several pigs were fed with the organism mixed with their regular diet for variable lengths of time (from three to fourteen days) and then killed at intervals of from two to eleven days. In none of these pigs was the *B. pyocyaneus* recovered when cultures were taken from the different parts of their intestinal tract and stomach (Table 2).

TABLE 2.—Results in Pigs Fed on Normal Diet of Oats, Hay, Bread and Green Stuff. B. Pyocyaneus Mixed with This Normal Diet for Variable Lengths of Time. Normal Diet Continued Until Pigs Were Killed or Died

No. Days Pigs Fed	Killed or Died	Day Killed or Died	Heart Culture	Stomach Culture	Duodenum Culture	Ileum Culture	Cecum Culture	Colon Culture
2	K	1	.....	0	0	0	+	
2	K	2	.....	0	0	.....	+	
2	K	4	.....	0	0	0	0	
3	K	4	.....	0	0	0	0	0
3	K	5	.....	0	0	0	0	
3	K	6	N.G.—0	0	0	0	0	0
3	K	7	.....	0	0	0	0	0
3	K	8	N.G.—0	0	0	0	0	0
3	K	9	N.G.—0	0	0	0	0	0
3	K	11	N.G.—0	0	0	0	0	
7	K	3	.....	0	0	.....	0	
14	K	2	N.G.—0	0	0	0	0	0

Day killed or died, i.e., day after last ingestion of pyocyaneus. In the columns showing the results of culture, a blank indicates that no culture was taken; 0 indicates that there was no growth of pyocyaneus; N.G. indicates that there was no growth or any type of organism; + indicates a growth of pyocyaneus.

The thought presents itself as to whether or not much of the pyocyaneus is ingested when the organism is mixed with the regular diet of oats, bread and water, hay and green stuff. It will be remembered that in eating the whole oat the pig cracks open the outer covering of the oat kernel, discards this covering and eats the softer center. By using rolled or crushed oats the culture of *B. pyocyaneus* can be mixed thoroughly with the food. Accordingly, four pigs were fed in this manner. First, they were given a two-day diet of rolled oats without pyocyaneus. This was to accustom them to their diet, or

at least to assure sufficient hunger so that during the three following days in which the *B. pyocyaneus* was fed a considerable amount of the germ-mixed food would be ingested. On discontinuing the feeding of the organism, the regular diet was instituted. The *B. pyocyaneus* was not recovered from any of the pigs of this series when killed at intervals of from five to eleven days later. On the normal diet, *B. pyocyaneus* does not, then, persist in the digestive canal.

Several other experiments were carried out, the details of which need not be given. Briefly, they consisted in feeding series of pigs on a simple died of oat kernels and water. In some of these series the attempt was made to assure the ingestion of the bacillus by mixing it with oats and water eighteen hours or less before feeding. It was found that the organism did not always live under such circumstances.

TABLE 3.—PIGS FED ROLLED OATS FOR ONE WEEK; THEN ROLLED OATS PLUS B. PYOCYANEUS FOR FROM ONE TO THREE DAYS. A DIET OF ROLLED OATS WAS THEN CONTINUED. THREE CONTROLS NOT FED B. PYOCYANEUS DIED AT EIGHT, EIGHT AND FIFTEEN DAYS, RESPECTIVELY

No. Days Pyo. Fed	Killed or Died	Day Killed or Died	Heart Culture	Stomach Culture	Duodenum Culture	Ileum Culture	Cecum Culture	Colon Culture
3	D	2	+++	+++	.....	.....	++	
3	D	2	N.G.—0	+++	.....	.....	+++	
3	D	3	N.G.—0	0	0	.....	++	0
3	K	5	N.G.—0	0	0	.....	0	0
3	K	7	N.G.—0	+++	++	0	++	+
1	D	1	N.G.—0	0	0	0	0	0
2	D	2	N.G.—0	++	++	++	+++	++
3	D	3	+++	+++	N.G.—0	+++	+++	+++
2	D	4	N.G.—0	++	++	++	0	
3	D	3	N.G.—0	+	0	++	+++	0
2	K	7	.....	0	N.G.—0	0	0	N.G.—0
2	K	9	.....	0	0	.....	0	0
3	K	9	.....	+	++	.....	0	0
3	K	9	.....	0	0	0	0	0

\+ Indicates a slight growth of pyocyaneus.
++ Indicates a more active growth.
+++ Indicates a large amount of growth.

In order to remove doubt as to whether the *B. pyocyaneus* was ingested because of the failure of the pigs to eat an abnormal diet, such as rolled oats, a number of pigs were fed *B. pyocyaneus* only after they had been previously fed on rolled oats alone for a week. Over 50 per cent. of the fourteen pigs in this series died.[10] We believe that it is seldom, if ever, that guinea-pigs die as the result of the ingestion of *B. pyocyaneus* when mixed with the food, but that death is due rather to the lack of essential elements in the limited diet. It will be seen later that the addition of green stuff to the rolled oats partly overcame this difficulty, and that only four of fifteen pigs

10. Three control pigs that were fed simply on rolled oats and water without at any time the admixture of *B. pyocyaneus* died at eight, eight, and fifteen days, respectively, after the institution of the régime.

(about 25 per cent.) died. It is probable from the necropsy findings and the cultures that at least two of these four pigs died from an infection with an organism of the paratyphoid group. *B. pyocyaneus* was recovered from the gastro-intestinal tract of nine of the fourteen pigs (Table 3). Three of these nine pigs died two days after the cessation of pyocyaneus feeding; three died three days after; one died four days after; one was killed seven days after and one was killed nine days after. Of the five pigs in which the *B. pyocyaneus* was not recovered one died at the end of the first day after the attempt to feed *B. pyocyaneus* and this pig was apparently sick at the time with an infection by an organism of the paratyphoid group and did not eat the food mixed with the *B. pyocyaneus*. Of the other four, one was killed at the end of five days, one at seven days and ten at the end of nine days.

In the next experiment a small amount of green stuff was added each day to the rolled oats diet. *B. pyocyaneus* was recovered in all at the end of seven days after the cessation of *B. pyocyaneus* feeding, one was killed nine days after feeding ceased and one was killed thirteen days after feeding ceased. Of the pigs in which *B. pyocyaneus* was recovered, two died the first day after the cessation of pyocyaneus feeding; one was killed after five days; one was killed and one died after seven days; one was killed at eight days; three were killed at nine days; one was killed at ten days; one was killed at eleven days and one was killed at twelve days (Table 4).

TABLE 4.—Pigs Fed Rolled Oats Plus Green Stuff for Five Days; Then Rolled Oats Plus Green Stuff Plus B. Pyocyaneus for from Two to Three Days. A Diet of Rolled Oats and Green Stuff Then Continued

No. Days Pyo. Fed	Killed or Died	Day Killed or Died	Heart Culture	Stomach Culture	Duodenum Culture	Ileum Culture	Cecum Culture	Colon Culture
2	D	1	N.G.—0	+++	+++	.....	+++	+++
2	D	1	0	+++	+++	+++	+++	0
3	D	7	N.G.—0	+++	0	++	+++	+
3	D	10	N.G.—0	+	0	.....	++	++
3	K	5	+	0	N.G.—0	++	+	0
3	K	7	N.G.—0	0	0	0	0	
3	K	7	N.G.—0	N.G.—0	.....	0	+	N.G.—0
3	K	9	.....	0	0	0	+++	0
3	K	9	N.G.—0	+++	++	0	0	0
3	K	9	N.G.—0	0	0	0	+	
3	K	9	N.G.—0	0	0	0	0	0
3	K	9	N.G.—0	0	0	0	++	0
3	K	10	N.G.—0	+	0	.....	++	++
3	K	11	N.G.—0	0	0	0	++	0
3	K	12	N.G.—0	0	N.G.—0	0	+	0
3	K	13	N.G.—0	0	N.G.—0	0	+	0

Ten pigs were now fed rolled oats and butter for five days, then *B. pyocyaneus* was mixed with this food for three days and the rolled oats and butter diet continued thereafter. In all of this series *B.*

pyocyaneus was recovered from the digestive tract when the pigs were killed or died from three to thirteen days following the cessation of germ feeding. Five pigs died at three, four, seven, nine and ten days, respectively, and five were killed at five, five, seven, eleven and thirteen days respectively (Table 5).

TABLE 5.—PIGS FED ROLLED OATS PLUS BUTTER FOR FIVE DAYS; THEN ROLLED OATS PLUS BUTTER PLUS B. PYOCYANEUS FOR THREE DAYS. A DIET OF ROLLED OATS AND BUTTER WAS THEN CONTINUED

Killed or Died	Day Killed or Died	Heart Culture	Stomach Culture	Duodenum Culture	Ileum Culture	Cecum Culture	Colon Culture
D	3	N.G.—0	0	+	+++	+++	0
D	4	N.G.—0	0	0	.....	+++	N.G.—0
K	5	N.G.—0	N.G.—0	N.G.—0	.....	++	0
K	5	0	0	0	++	+++	+++
D	7	N.G.—0	++	++	0	++	++
K	7	0	0	0	N.G.—0	+	0
D	9	N.G.—0	+	+++	++	++	0
D	9	N.G.—0	++	++	0	+	0
K	11	N.G.—0	0	N.G.—0	.....	+++	0
K	13	N.G.—0	+	++	+	+	++

SUMMARY AND CONCLUSIONS

Bacillus pyocyaneus when fed to guinea-pigs nourished on a diet of oats, hay, bread and green stuff (the normal diet in this laboratory) usually disappears from the gastro-intestinal tract within three days. When oat meal is given as a sole article of diet, the *B. pyocyaneus* has been found at seven and nine days after the last administration. The addition of a small amount of green stuff, or of a certain amount of butter to the oatmeal diet, has apparently prolonged the period of persistence of the bacterium: *B. pyocyaneus* on these slightly amplified diets has been found to persist about two weeks with considerable regularity. This increased persistence is probably apparent only. The animals on a strict oatmeal diet do not live long enough to enable a complete experiment to be carried out much beyond eight or ten days.

Bacillus pyocyaneus could not be recovered from the digestive canal in any case more than sixteen days after the cessation of its ingestion by mouth. Judged by the amount of pigment produced in the culture, the number of surviving bacteria became progressively less the longer the time interval following the cessation of its ingestion by the pig. *B. pyocyaneus* persisted more readily in the cecum than in other parts of the digestive tract, next in the stomach, although it was often found on culturing the duodenum, ileum and colon. This was true whether the pigs were killed soon after the cessation of *B. pyocyaneus* feeding or only after a longer interval.

It is probable, on the basis of these experiments, that there is an effect of dietary deficiency which consists in the depression of a normal mechanism controlling the implantation of extraneous bacteria in the intestinal tract.

AN ANALYSIS OF TWO-HUNDRED AND FIFTY WARD CASES OF ACUTE ENDOCARDITIS IN CHILDREN *

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An endeavor is made in this paper to analyze a large series of cases of acute endocarditis treated in hospital wards, not so much for the purpose of imparting new information on a subject already much discussed, but to give briefly the etiology, symptoms, physical findings, treatment and immediate results of the treatment as they were recorded in these 250 cases. Only cases of acute endocarditis are included in this series. There are, however, a number of cases of acute exacerbations of chronic valvular disease which resulted from previous attacks of acute endocarditis. The severity of these cases varied considerably. There are seventy comparatively mild cases, which are grouped together as the "mild group." The remaining 180 cases are placed in the "severe group."

ASSOCIATED CONDITIONS AND PREDISPOSING CAUSES

Age.—Morse,[1] Holt [2] and Dunn [3] state that endocarditis is uncommon before the fifth year. In this series, 24.4 per cent. occurred before the fifth year. The greatest incidence, 38.8 per cent., was between the fifth and eighth years. In the group of patients between the ages of 8 and 13 years, there were twenty-three who gave a history of previous attacks occurring before the end of the eighth year, thus bringing the percentage occurring between 5 and 8 years up to 48 and reducing the primary attacks occurring between 8 and 13 years to 27.6 per cent.

Sex.—The sexes as a whole were almost equally affected. Below the age of 5 the males were slightly in the lead, while above 8 years the females took the lead.

Associated Diseases.—Several patients gave a history of tonsillitis, or chorea, or both, in addition to rheumatic fever. All of these I have classed as rheumatic fever. Other patients gave a history of chorea

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* From the records of the Children's Hospital and of the Massachusetts General Hospital of Boston.

1. Morse, J. L.: Boston M. & S. J. **161**:273, 1909.
2. Holt, L. E.: Textbook of Pediatrics, Ed. 7, New York, D. Appleton & Co., p. 594.
3. Dunn, C. H.: Textbook of Pediatrics, Troy, N. Y., Southworth Co., Vol. 3 p. 33.

and tonsillitis, which I have classed as chorea. By some writers all these conditions are classed with endocarditis, as different manifestations of the same infection. This theory cannot very well be disproved, as the causative agent in any of the conditions is not known, but the findings in this series of cases would tend to show that, at least, the virulence of the infection differs in the different manifestations. Endocarditis occurring with chorea is found to be much milder than that occurring with either rheumatic fever or tonsillitis: the mortality in the choreic group being only 2.8 per cent., while that of the rheumatic group is 17 per cent. and that of the tonsillitis group 10 per cent.

TABLE 1.—AGE INCIDENCE

Years	Cases	Per Cent.
Between 2 and 3	17	6.8
Between 3 and 5	44	17.6
Between 5 and 8	97	38.8
Between 8 and 13	92	36.8

TABLE 2.—SEX INCIDENCE

	Cases	Per Cent.
Male	120	48
Female	130	52

TABLE 3.—ASSOCIATED DISEASES

Disease	Cases	Per Cent.
Rheumatic fever	151	60.4
Chorea	36	14.4
Tonsillitis	30	12.0
Local sepsis	8	3.2
Influenza	4	1.6
Pneumonia	2	0.8
Scarlet fever	2	0.8
No known associated disease	17	6.8

Endocarditis in childhood is largely due to rheumatic fever infection, and it may occur as the first manifestation of that infection. In this series 151 cases, or 60.4 per cent., gave a history of rheumatic fever. In five of these the articular symptoms followed those of endocarditis. Very severe endocarditis may accompany the mildest articular manifestations of rheumatic fever. Five of the fatal rheumatic cases gave a history of very slight articular pains. In seventeen cases there was no history of rheumatic fever, chorea, tonsillitis or other infectious disease. It seems quite probable that these were largely rheumatic cases; the rheumatic pain being so slight that it was unnoticed by the patient. Six of these seventeen patients died, thus showing the severity of this class of cases.

It seems reasonable to believe that the severity of endocarditis, occurring with the mild articular symptoms, can be accounted for by the fact that the patient is not confined to bed by the articular symptoms. Often he is up and about, and in some instances takes violent exercise and becomes aware of disease only when the cardiac symptoms appear; the heart structure being, therefore, severely taxed at a time when the inflammation in the endocardium is at its height.

Thirty-six cases, or 14.4 per cent., gave a history of chorea. This is a much smaller percentage than has been found by many investigators. Eustis [4] reported that 70 per cent. of his cases were associated with chorea. He included all the cases which gave a history of chorea. Holt, in a series of 117 cases, reports 30 per cent. occurring with chorea.

Tonsillitis was the only associated condition found in thirty cases, or 12 per cent. It was present, however, in the majority of the choreic and rheumatic cases. Eight cases, or 3.2 per cent., were associated with local sepsis, including cervical adenitis, osteomyelitis and empyema. Pneumonia was found to be the only associated condition in two cases and both these patients recovered. Four cases, or 1.6 per cent., gave a history of influenza. These were very severe cases, two proving fatal. Two cases were due to scarlet fever and both these patients recovered.

SYMPTOMS

There were 104 patients, or 41.6 per cent., who did not at any time complain of any symptoms relative to the heart. These cases came into the doctor's care because of associated diseases, such as chorea, tonsillitis, etc. The most constant symptoms complained of were dyspnea, precordial pain, palpitation and epigastric pain. Dyspnea was a marked symptom in 115 cases, or 46 per cent. Precordial pain was present in forty-four cases, or 17.6 per cent. Thirty-one patients, or 12 per cent., complained of epigastric pain. Palpitation was complained of by only fourteen patients, or 5.6 per cent. Sixty-one per cent. of the rheumatic group, 56.6 per cent. of the tonsillitis group, 19.4 per cent. of the choreic group and 90 per cent. of the remaining groups complained of cardiac symptoms. Twenty-one per cent. of the patients classed in the mild group and 72.7 per cent. of those in the severe group complained of cardiac symptoms.

Temperature.—The temperature was found to be very irregular in the majority of cases. I have, therefore, tabulated each patient's average temperature during the febrile period of the disease. The temperature of the group as a whole was very moderately elevated, the average being 99.8 F.

The average temperature for the severe group was 100 F., that of the mild group 99.1 F., that of the fatal group 100.3 F.

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4. Eustis, R. S.: Boston M. & S. J. **173**:348, 1915.

In the severe group, 55 patients had an average temperature of 99 F.; 74 had 100 F.; 32 had 101 F.; 15 had 102 F.; 4 had 103 F.

In the fatal group 12 patients had an average temperature of 99 F.; 10 had 100 F.; 5 had 102 F.; 1 had 103 F.

In the mild group there were only fourteen patients with a temperature of 100 F., or above. The average duration of the febrile period in the severe group was more than double that of the mild group, being thirty-six days in the severe group and seventeen days in the mild group. The duration of the febrile period was longer in the older patients, as shown in the following table:

Age	Duration, Days
Below 3 years	18
Between 3 and 5 years	27
Between 5 and 8 years	35
Between 8 and 13 years	47

Pulse Rate.—The pulse rate in individual cases was found to be very irregular. I have, therefore, tabulated each patient's average pulse rate during the febrile period (Table 4).

TABLE 4.—Pulse Rate in Various Groups

Number of Patients	Pulse Rate per Minute
Mild Group:	
55	90
11	100
4	120
Severe Group:	
44	100
21	110
50	120
36	130
15	140
Fatal Group:	
3	100
1	110
14	120
15	130
4	140
3	150

Cardiac Enlargement.—In recent years the diagnosis and prognosis of heart disease is largely made from one finding, cardiac enlargement. Therefore the importance of this sign has stimulated a desire for more accurate means of determining the outlines of the heart. Much has been done with the roentgen rays to check up percussion findings, and to perfect a method of obtaining accurate outlines.[5] Although it has been proven by roentgen-ray interpretations that percussion outlines

5. Shattuck, G. C.: Boston M. & S. J. **174**:301. Holmes, G. W.: Med. Clin. N. America **1**:1197, 1916.

are often erroneous in adults, this is not true with children, if their chest walls are not deformed. Children have comparatively thin chest walls, and percussion is, therefore, less difficult and more accurate than in the chests of adults. In this series percussion was used entirely for locating the cardiac outlines. I have tabulated only the greatest transverse diameter of relative cardiac dullness. For the purpose of comparison I will first give the normal diameters as they are found at various ages.[6] The normal transverse diameter of relative cardiac dullness in infancy is from 7 to 8 cm.; at 6 years it is 9.5 cm., and at 12 years it is 11 cm. The transverse diameter of relative cardiac dullness, as found in the various groups of this series, is shown in Table 5.

TABLE 5.—Transverse Diameter of Relative Cardiac Dulness

Group	Below 6 Years		Between 6 and 8 Years		From 8 to 13 Years	
	Diameter, Cm.	Cases	Diameter Cm.	Cases	Diameter, Cm.	Cases
Mild	9	6	10	13	10	10
	10	3	11	5	11	12
	11	2	12	2	12	10
	13	1	14	1	13	1
					14	4
Average	10		10.7		11.4	
Severe	9	12	9	3	9	2
	10	17	10	6	10	6
	11	17	11	12	11	12
	12	8	12	15	12	13
	13	4	13	16	13	13
	15	4	14	3	13	8
			15	2	14	3
					15	2
					16	2
					18	2
Average	10.6		12		12.5	
Fatal	9	2	12	2	10	2
	10	3	13	5	13	4
	11	3	14	2	14	4
	12	5	15	1	15	2
	13	2	18	1	18	1
	15	1				
Average	11.5		13.5		13.7	

White Blood Count.—The leukocyte count in this series varied greatly. While the increase was marked in some cases, there were others in which the absolute counts showed little or no deviation from the normal. A reason for this apparent incongruity was not always manifest, but as a rule, the degree of severity of the infection, together with certain etiologic factors, determined to a large extent the amount of leukocytosis. I have been unable to find very much in medical literature concerning the reaction of the leukocytes in endocarditis.

6. Taken from Morse's Case Histories in Pediatrics, Ed. 2.

Cabot,[7] in a series of twenty-six cases, which he termed acute ulcerative endocarditis, found the initial leukocyte count below 10,000 in six cases, between 10,000 and 15,000 in five cases, and above 15,000 in fifteen cases. The lowest count was 3,000 and the highest 34,000.

In another series of fourteen cases, which he called benign endocarditis, he found the leukocyte count much higher than in the ulcerative group just cited. In this group the count was below 15,000 in only one case, betweeen 15,000 and 20,000 in three cases, and above 20,000 in the remaining ten cases, the lowest count being 12,000 and the highest, 50,100. These extremely high counts occurring in cases of simple endocarditis must have been due to some associated infection outside of the heart. Unfortunately, systematic counts in large series are not available.

TABLE 6.—AVERAGE INITIAL COUNT

	Leukocytes
For the whole group of 250 cases	17,200
Below 5 years	18,000
Between 5 and 13 years	17,000
Mild group	13,400
Severe group	19,000
Fatal group	21,000
Rheumatic group	18,000
Tonsillitis group	17,000
Chorea group	11,900
Undetermined group	17,000
Scarlet fever group	14,500
Local sepsis group	22,100
Pneumonia group	28,000
Influenza group	24,000

TABLE 7.—INDIVIDUAL LEUKOCYTE COUNTS

Patients	Per Cent.	Leukocytes
Mild Group:		
23	33	Below 10,000
45	64	Between 10,000 and 20,000
2	3	Above 20,000
Severe Group:		
23	12.5	Below 10,000
93	52	Between 10,000 and 20,000
64	35.5	Above 20,000
Fatal Group:		
0	0.0	Below 10,000
11	27.5	Between 10,000 and 15,000
5	22.5	Between 15,000 and 20,000
20	50	Above 20,000

It is shown by Table 6, first, that the degree of leukocytosis in acute endocarditis is considerably increased; second, that the count in the cases which are classed as severe, is almost one and one-half times that of the cases classed as mild.

Table 7 presents the individual counts as recorded in the various groups.

7. Cabot, R. C.: Clinical Examination of the Blood, Ed. 5, New York, William Wood & Co., p. 347.

These figures show that the leukocyte count is much higher in the severe cases. The few high counts in the mild cases may be accounted for by associated local sepsis, or other associated infections. The low counts recorded in the severe cases are probably due to an overwhelming infection.

It is interesting to note that, among the fatal group, there were no counts below 10,000 and 50 per cent. were above 20,000. The extremely low count in the choreic group is very striking, it being only slightly above normal and a little less than two-thirds as high as the count in the rheumatic fever group. The degree of leukocytosis was not influenced to any appreciable extent by the age of the patient; neither was it affected to a great extent by the degree of fever.

Valvular Involvement.—Endocarditis in children nearly always affects the mitral valve. The aortic valve is affected much less frequently, and is usually accompanied by mitral involvement. Any one or all the valves of the heart may be involved, but in this series there was no instance in which the pulmonic valve showed any physical signs of involvement. There was only one case in which the tricuspid valve was involved and this occurred in a girl, aged 3½ years. She had a severe attack of tonsillitis with rheumatic fever, and died four days after entering the hospital. The mitral valve was also involved in this case. In this series of 250 cases the mitral valve was involved in every instance, and the aortic in thirty-seven instances.

Dunn,[8] in a series of 262 cases of chronic valvular disease of the heart, found the aortic valve alone involved in one instance, and twelve cases in which both the aortic and mitral valves were involved, and no case with tricuspid inolvement. Wentworth,[8] in a series of 600 heart cases, found fifteen of aortic involvement, two of which were not associated with any other lesions, and one instance of tricuspid involvement. In 150 necropsies on children dead of cardiac disease, Poynton [9] found the mitral valve involved in 149 instances and the aortic in fifty-one instances. Fifty per cent. of the cases with aortic involvement were among the fatal cases in this series.

When discharged from the hospital, there were only two cases which did not have a cardiac murmur. Pericarditis occurred in 32 patients, or 12.8 per cent. Seventeen, or 53 per cent. of this number died. Both the aortic and mitral valves were involved in fifteen instances, or 47 per cent. The etiology was rheumatic fever in twenty-five cases, tonsillitis in one case, and influenza in one case. Six cases, or 19 per cent., occurred before the fifth year, and twenty-six cases occurred between 5 and 15 years.

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8. Wentworth, M. H.: Boston M. & S. J. **174**:158, 1917-1918.
9. Poynton, M. J.: Brit. M. J. **2**:147, 1918.

FACTORS BEARING ON PROGNOSIS

Age.—It is generally conceded that the earlier the primary endocarditis occurs, the better is the ultimate prognosis, because of the more perfect adaptation of the child to the heart, and the heart to the child; that they grow up together, and are more apt to adapt themselves to each other than they are in later life. The immediate prognosis, however, is much worse in the younger children. The immediate mortality in this series, as a whole, was 16 per cent.; below the third year, it was 30 per cent.; below the fifth year, 23.7 per cent.; between the fifth and thirteenth years 13.7 per cent., thus showing a decreasing mortality with increasing age of the patient.

Sex.—Sex did not seem to influence the severity of the infection, the fatal cases being about equally divided between the sexes.

The type, severity and duration of the infection of the heart itself, influence the prognosis very greatly.

The immediate mortality in the various groups was as follows: acute rheumatic fever, 17 per cent., tonsillitis, 10 per cent., chorea, 2.8 per cent. It appears, therefore, that endocarditis occurring with chorea and not associated with rheumatic fever is very mild, rarely producing death, while in rheumatic fever the prognosis depends on the severity of the cardiac infection. All grades of severity are met with in rheumatic heart infection. A simple rheumatic infection may lead to a slight crumpling of a valve and a soundly healed scar, the process becomes stayed, the heart muscle remains intact, and the heart for practical purposes is little or no worse than a normal heart. A further degree shows mere destruction and greater regurgitation, with involvement of the heart muscle. The next degree is that of repeated acute infection or chronic continuous infection, leading to stenosis and to serious carditis.

How are we to determine the intensity of cardiac infection? European writers are inclined to believe that all diseased hearts become enlarged, that no heart is diseased unless it is enlarged, that the mere regurgitation of blood is insufficient to give rise to dilatation and hypertrophy of the heart, and, therefore, they disregard all apical systolic murmurs unless they are accompanied by cardiac enlargement, the degree of enlargement being proportionate to the intensity and duration of the infection.

Fever.—The height of the fever is not a sure index of the severity of the cardiac infection. The duration of the fever is very significant, however. An early permanent return of the temperature to normal is a very favorable sign. A long duration of fever means that the heart is working under great stress, and that the damage to the heart muscles, especially to the conducting paths, to the interventricular nodes and to

the bundle of His, is in proportion to the duration of the fever. In this series, although the average temperature of the severe and fatal groups was less than one degree higher than that of the mild group, yet the average duration of the fever in the severe group was three times that of the mild group.

Pulse Rate.—The pulse rate is usually higher in the severe cases, but may be as low as 100, even in fatal cases.

Leukocytosis.—Leukocytosis is usually greater in the severer cases, but may occasionally be very slight in cases of marked severity. The average leukocyte count in the severe group was one and one-half times that of the mild group. The process in the heart should be considered active until the leukocyte count has reached normal. Simple mitral regurgitation, without stenosis, may leave the heart little or not at all damaged.

Stenosis.—When stenosis is present, a long continued infection or an often repeated acute infection has already wrought much damage to the heart muscle, the functional efficiency of the heart muscle is much lowered and the ultimate prognosis is, therefore, very unfavorable.

When both aortic and mitral valves are involved, the immediate prognosis is bad and the ultimate prognosis is very much worse.

Heart Failure.—When there are objective signs of heart failure, such as dropsy, enlarged liver and orthopnea, which do not disappear, the patient's future may be recorded in months.

Finally, it is to be clearly recognized, that each case requires special study. The personal element and the patient's daily routine enter largely into the composition of the disease picture. It is manifest, for example, that an impaired heart in the child who has a comfortable home and may lead a life of leisure has a significance different from that of an impaired heart in a child compelled to lead a strenuous and poorly directed life.

TREATMENT

The treatment in these cases consisted largely of rest in bed. Everything else was considered subordinate. The patients were kept as nearly flat in bed as possible, judgment being used in this connection, however, because being kept flat may cause so much fretting and fussing that more strain will be brought on the heart than if the patient is allowed to sit up in bed and play with toys. The severely ill patients were not allowed to feed themselves but were fed in order to prevent even that slight exertion. If there was severe dyspnea or orthopnea, they were propped up with pillows so that they might assume the most comfortable position. There was not a set period of time for all patients to remain in bed, this being determined in each individual case by the duration of the symptoms and the reaction of the heart to exer-

cise. When the temperature had become normal and the cardiac symptoms showed that the acute infection had subsided, the strict rest treatment was very gradually relaxed, the patient being observed closely.

When the acute symptoms had definitely and permanently subsided the patients were discharged from the hospital. The patients in whom the symptoms were slightly active were sent to institutions especially provided for their care. The patients with inactive lesions were discharged home to be followed up by the social service and seen at frequent intervals by the out-patient department of the hospital.

For two or three months the patients were given a limited amount of exercise, being kept in bed the greater part of the time. During the next one or two years the amount of exercise was limited, and finally an effort was made to plan the whole life so as to save the heart.

The nutrition and physical condition were kept in the best possible state, because the nutrition of the heart muscle depends to a considerable extent on the general nutrition.

The patients in the mild group were kept in bed in the hospital an average of 30.5 days, and those in the severe group an average of 50 days.

The general measures of treatment employed in the hospitals were those for acute infectious diseases in general. The bowels were kept open, and the diet consisted at first of milk and starchy foods; later meat and eggs were allowed. In cases occurring with acute rheumatic fever, acetyl salicylic acid was given freely. Digitalis was used very infrequently, being given only in the cases of chronic valvular lesions with failure of compensation. It was not given in cases of simple acute endocarditis. Sedatives were used when demanded. When the heart was irritable and the action rapid, and especially if there was precordial pain, an ice bag was applied over the heart. Other symptoms were treated as they arose.

When the focus of the infection could be located, it was, as a rule, removed before the patient was discharged from the hospital. It was difficult sometimes to determine just when the focus should be removed. If the acute symptoms gradually cleared up with the focus present, it was not removed until the acute symptoms had subsided. If it was thought, however, that the local focus was keeping the acute symptoms active over an extended period of time, and the condition of the patient was not too bad, the focus was removed. The teeth and tonsils were the most frequent local foci of infection. Ether anesthesia was administered without hesitation for tonsillectomies and for teeth extraction, when necessary. No bad results occurred so far as the heart was concerned.

IMMEDIATE RESULTS OF HOSPITAL TREATMENT

One hundred and six patients, or 42.4 per cent., were discharged home, without active symptoms, to be supervised and cared for by the Social Service and the Out-patient Department of the hospitals. Sixty-seven patients, or 26.8 per cent., were discharged with slightly active symptoms, to institutions provided for this class of cases. Thirty-seven patients, or 14.8 per cent., were discharged against advice with active symptoms. This demonstrates the difficulty in obtaining the cooperation of the parents so necessary in the prolonged treatment of this disease. The remaining forty patients, or 16 per cent., died

STUDIES IN SPASMOPHILIA

III. BLOOD CALCIUM AND CALCIUM THERAPY IN OLDER CHILDREN WITH THIEMICH'S SIGN *

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We are now perfectly familiar with the low calcium content of the blood in tetany. MacCallum and Voegtlin [1] were the first to demonstrate this in parathyroidectomized dogs; MacCallum and Vogel later confirmed it [2] and the fact was conclusively shown in infantile tetany by Howland and Marriott [3] in 1918. Since that time many investigators have confirmed these results. We are also familiar with the effect of calcium therapy on the blood calcium and the electrical reactions of tetany.

Stheeman [4] reported low blood calcium in older children with anodal reactions of Thiemich, but, as previously pointed out,[5] his method of calcium determination was faulty and his findings inconstant. Howland and Marriott [3] have determined the serum calcium of infants with anodal hyperexcitability but without tetany, and found the average value for twelve cases to be 9.25 mg. per 100 c.c., which is slightly below their normal value of from 10 to 11 mg. Ten of these children, however, had rickets, and they state that in rickets one finds a slightly reduced serum calcium. In fact, the only patients in this group who did not have rickets had 10.7 mg. calcium each.

In the effort to establish the significance of so-called anodal hyperexcitability reactions in older children, blood calcium was determined in such cases and the electrical reactions were studied before and after repeated large amounts of calcium feeding. The problem is not, how-

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* The blood calcium analyses were carried out by me in the pathological laboratory of the College of Physicians and Surgeons of New York City, and I wish to thank Prof. J. W. Jobling for extending me this privilege.

1. MacCallum, W. G., and Voegtlin, Carl: On the Relation of Tetany to the Parathyroid Glands and to Calcium Metabolism, J. Exper. M. **11**:118 (Jan.) 1909.

2. MacCallum, W. G., and Vogel, K. M.: Further Experimental Studies in Tetany, J. Exper. M. **18**:618 (Dec.) 1913.

3. Howland, J., and Marriott, W. McK.: Observations on Calcium Content of Blood in Infantile Tetany and on the Effect of Treatment by Calcium, Quart. J. M. **11**:289 (July) 1918.

4. Stheeman, H. A.: Spasmophilia of Older Children, Jahrb. f. Kinderh. **86**:42, 1917.

5. Von Meysenbug, L.: Studies in Spasmophilia. II. Electrical Reactions of Older Children, Am. J. Dis. Child. (to be published).

however, as simple as it would appear to be at first glance. There are several complicating factors. The first of these is the fact that the blood calcium may be as low as 7.0 mg. per 100 c.c. serum without tetany appearing, as shown by Binger [6] experimentally, and corroborated by the findings of Howland and Marriott clinically. When the blood calcium fell below this level tetany supervened. Furthermore, Denis and Minot [7] have pointed out that it is impossible to increase the blood calcium by massive calcium feeding when the initial value is normal. It would seem most unlikely, therefore, that calcium feeding would influence the electrical reactions if these accompany a normal blood calcium.

TABLE 1.—CONTROLS. CALCIUM EXPRESSED AS MG. PER 100 C.C. PLASMA

Age, Yrs.	Date, 1920	C C C	A C C	A O C	C O C	Calcium
4	March 23	2.0	>5	>5	>5	11 3
4	March 23	2.0	3.0	>5	>5	11.5
5	March 26	2.5	>5	>5	>5	11.1
1	March 30	2.6	>5	>5	>5	11.5
5	April 6	2.0	4.0	>5	>5	10.7
Average	.....	.....	...	...	...	11.2

TABLE 2.—THIEMICH'S SIGN. CALCIUM EXPRESSED AS MG. PER 100 C.C. PLASMA

Age, Yrs.	Sex	Date, 1920	C C C	A C C	A O C	C O C	Calcium
4	♂	March 23	0.6	2.0	1.4	>5	10.3
5	♂	March 26	1.6	3.0	3.0	>5	10.7
½*	♀	March 26	0.2	1.0	1.0	2.0	11.5
5	♂	March 26	1.4	4.8	2.5	>5	10.9
3	♂	March 27	1.2	3.2	2.4	>5	11.3
2	♀	March 27	1.0	4.5	2.0	>5	10.0
5	♀	March 30	0.6	2.0	1.4	>5	11.4
4	♂	March 30	1.6	3.4	2.4	>5	11.5
1†	♂	March 30	1.4	3.0	1.8	>5	8.7
6	♀	April 2	1.2	3.0	1.6	>5	10.2
5	♀	April 2	1.2	3.2	1.6	C C T 4	11.3
4	♀	April 2	1.6	3.4	3.2	>5	11.7
Average.....							10.8

* Rickets. † Slight rickets.

BLOOD CALCIUM

The cases which I selected were those showing the most marked Thiemich's and Chvostek's signs. The calcium was determined by Lyman's method on citrated plasma.[7] A group of five children with very low electrical irritability was selected as controls.

Table 2 shows the electrical reactions and plasma calcium of twelve children with Thiemich's sign. It is interesting to note that one of

6. Binger, C.: Toxicity of Phosphates in Relation to Blood Calcium and Tetany, J. Pharmacol. & Exper. Therap. **10**:105 (Aug.) 1917.

7. Denis, W., and Minot, A. S.: Effects of Feeding with Calcium Salts on the Calcium Content of the Blood, J. Biol. Chem. **41**:357 (March) 1920.

the highest calcium values found was in an infant 6 months old, with very marked spasmophilic reactions, but without tetany. Five months previously this infant had had convulsions and laryngospasm. The difference between the average values of Table 1 and Table 2 is too slight to be of any significance.

CALCIUM THERAPY

Two children, whose plasma calcium was found to be 10.3 and 11.4 mg. per 100 c.c. respectively (Nos. 1 and 7 in Table 2) were chosen because of the older children they showed the highest electrical irritability and both had very marked Chvostek signs. Table 3 shows the results. S. W. appears to be somewhat improved March 23, after three consecutive days of calcium feeding, but the change is not greater than might be expected in the variation of the reactions from day to day. The reactions of H. T. remain practically constant throughout. The constancy of the plasma calcium is well shown by the analyses on H. T., one taken during the feeding period of massive doses of calcium, the second a week after the calcium had been omitted.

TABLE 3.—CALCIUM LACTATE BY MOUTH

Name, Age and Sex	Date, 1920	C C C	A C C	A O C	C O C	Therapy	Plasma Calcium, Mg. per 100 C.c.
H. T.	March 9	1.0	3.4	2.0	>5		
4 yrs.	March 15	1.2	3.0	2.0	>5		
♂	March 15	...	...	...	...	6.0 gm. daily	
	March 16	1.0	2.4	1.6	>5	6.0 gm. daily	
	March 17	1.2	2.8	1.8	>5	6.0 gm. daily	
	March 18	1.0	2.0	1.6	>5	6.0 gm. daily	
	March 19	...	...	...	...	Omitted	
	March 20	0.6	2.2	1.6	>5	6.0 gm. daily	
	March 23	0.6	2.0	1.4	>5	6.0 gm. daily	10.3
	March 30	1.0	2.4	2.0	>5	Omitted March 23	10.4
S. W.	March 9	0.8	2.0	1.6	>5		
5 yrs.	March 15	1.4	2.0	1.6	>5		
♀	March 15	...	...	...	...	6.0 gm. daily	
	March 16	1.2	2.0	1.4	>5	6.0 gm. daily	
	March 17	1.0	2.1	1.5	>5	6.0 gm. daily	
	March 18	0.8	2.0	1.2	>5	6.0 gm. daily	
	March 19	1.2	2.0	1.8	>5	Omitted	
	March 20	0.8	2.0	1.4	>5	6.0 gm. daily	
	March 23	1.6	2.4	2.0	>5	6.0 gm. daily	
	March 30	0.8	2.0	1.4	>5	Omitted March 23	11.4

SUMMARY

1. Plasma calcium was determined by Lyman's method on five children with very low electrical irritability and on twelve children with Thiemich's sign. The average value for the first group was found to be 11.2 mg. per 100 c.c., for the second group 10.8 mg. per 100 c.c.—an insignificant difference.

2. Calcium lactate in 6.0 gm. daily doses was fed to two children with Thiemich's sign without resultant change in the electrical irritability.

CONCLUSIONS

1. Thiemich's sign in older children is not based on lowered blood calcium.

2. Calcium feeding in large amounts does not influence the anodal reactions of older children.

RUMINATION IN CHILDREN *

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REPORT OF CASE

History.—William L., born Oct. 6, 1918, is the only child of healthy though nervous parents. The mother is a pianist. Allaitement mixté during the first five months of life; then cow's milk alone for one month. At the age of 6 months, beef soup was repeatedly tried, but soon discontinued because with fits of anger he would persistently refuse it or spit it up. However, cereals, vegetables and fruits were taken well. At the age of nine months, beef soup was tried again and well taken and borne, if mixed with a little milk. There was never any other difficulty in feeding, except that even at the present time soup is disliked. Appetite, digestion and sleep always have been good.

At the age of 15 months (about Christmas, 1919) the boy began to spit up the orange juice that he was wont to take daily since his fourth month of life and of which he was very fond. At this time there was much drooling. At first the spitting up occurred only occasionally, but later it occurred frequently. Then the mother noticed that the boy would reswallow the orange juice after it had come up into the mouth, and that he seemed to enjoy it. He would even put his fingers into the vomitus on the floor and re-introduce it into the mouth. Two months later also other food was "spit up" after almost each meal. The food would ascend into the mouth in small portions without difficulty, violence or nausea, about five minutes after the meal and after a few masticatory movements be reswallowed. A minute or so later it would reappear, and the repetitions of the act were kept up for one hour or longer, also during his playtime. There was little food lost in this process. Parts of food that happened to spill over the clothes were put back by him into his mouth with his fingers. There was no doubt but that the boy enjoyed ruminating. The food brought up never had any odor. After dinner, when the boy used to remain alone and awake for a longer period, there was usually an aggravation of rumination and it also was observed that the "spitting up" became worse whenever the father coughed and belched in the boy's presence, who also manifested a great imitative tendency. On the other hand, rumination was less likely to occur after breakfast when the boy was usually entertained and diverted by his father's fondling and playing with him; or when he was outdoors, which he enjoyed. His appetite and digestion during this whole time was perfect.

The boy is very well nourished, sturdy looking, has red cheeks, weighs at present (at the age of 18 months) 25 pounds, but is very willful, nervous, timid, easily startled and scared by noises and overcautious toward strange persons and objects. His mother considers him a very intelligent though "very queer" child.

Treatment.—Naturally the observation of the influence of psychic elements on his rumination suggested distraction in a systematic manner as a therapeutic measure. In order to deflect his attention intensely and permanently from his affliction various means had to be employed, as exemplified in the following procedures.

March 30, the first day of treatment: Soon after the breakfast, at 6:15 a. m., he began to ruminate as usually. This was immediately stopped when the mother energetically scolded and threatened him. She then sang to him

* Received for publication Aug. 5, 1920.

and got him to sing with her for awhile; thereafter she amused him by questions that he would answer and continued diverting his mind by dressing him. Then the father undertook his amusement so that the boy's mind was permanently occupied for one whole hour. No rumination had occurred. At 10 a. m., after the bath, the boy was fed and put to bed where he fell asleep immediately without rumination. The next feeding was at 1:15 p. m. Immediately thereafter he was amused for about the first ten minutes by songs, in which he eventually joined. Thereafter he was given a new plaything, the novelty of which interested him intensely for awhile. When the novelty began to wear off, he was taken outdoors, which had been observed to have a tendency to lessen his rumination as stated before, no doubt likewise through diversion. No rumination occurred.

At 4:45 p. m. water and orange juice were given. The mother at once sang to him and played on the piano, of which he always has been very fond, and later she played with him. No rumination occurred.

Supper was at 5:30 p. m. He soon ruminated three times, but stopped when scolded. Talking to or continuously playing with him prevented him from ruminating entirely until he finally was put to bed and fell asleep immediately.

During the following few days identical pedagogic-therapeutic procedures were taken. March 31 rumination took place four times after dinner and once after supper. April 1 and 2 it occurred only once after supper. Since that time he has never ruminated or regurgitated. But he began chewing his sleeves or other parts of his garments within reach of his mouth.

In this case the persistent vomiting and regurgitating of soup with angry refusals, apparently due to aversion to it, may be taken as an early symptom of a certain lability of the reflex mechanism of the pharynx, esophagus and stomach under conditions that point to the interference of a psychoneurotic element. The psychic factor also revealed itself by the fact that later, coloring the soup with a little milk induced this very willful, undoubtedly nervous boy to take it without further trouble. There was never any other disturbance of the gastro-intestinal tract. No doubt the responsiveness of the reflex apparatus rendered it possible that later the regurgitation of orange juice, perhaps at first accidental, should have repeated itself with such readiness, in the beginning only occasionally, but soon regularly. The juice being agreeable to him, he apparently learned to reswallow it readily. Such a selective regurgitation of a particular food is well known in the adult ruminant. By frequent repetitions of this process aided by the psychic factor, through facilitation of the nervous centers involved, regurgitation and reswallowing became a pathologic, well fixed nervous habit, a pathologic reflex, easily started and finally released also for gratification by other food. It is not without significance that after the cure the boy, in order to obtain some gratification, found a substitute in chewing his sleeves, for several weeks.

The conception of pathologic conditional reflexes in the sense of Czerny and Ibrahim brings rumination nearer our understanding;

their nature and development was dwelt on by me in a former article.[1] The abnormal motor process of a pathologic condition reflex often originates from local pathologic causes but nevertheless persists even after the subsidence of the primary pathologic stimulus as a kind of pathologic habit of the nervous system. The acts are then provoked by the physiologic stimuli of the daily life. A conditional reflex can be traced to the cooperation of a psychic factor with an ordinary unconditional reflex. There is no definite or characteristic anatomic basis for rumination and its essential initial phase, the regurgitation.

The few fluoroscopic examinations made in babies have demonstrated no gross deviations from the normal and findings of pylorospasm as in the cases of Lust [2] and Aschenheim and in the one reported by me have only an indirect though important bearing. In such circumstances the rumination develops most probably as a secondary functional affection in consequence of the vomiting and regurgitating caused by these diseases. Similarly, "habitual vomiting" and pure regurgitation and vomiting due to chronic dyspepsia, especially often following ablactation, have been complicated by pronounced rumination. The original disturbance, anatomic or functional, sometimes, perhaps, very insignificant and thus easily overlooked, may act merely as an initial factor in the evolution of the pathologic complex of rumination. The members of the motor chain become firmly linked together as a complex and fixed through repetition and facilitation, possibly aided by the desire for gratification that lies in rumination, and may outlast the original affection, appearing then as an independent "neurosis."

The cooperation of an organic and neuropsychic component, combined in varying proportions, may be unmistakable in the development of rumination. In a number of cases it must be admitted, as Landé [3] has pointed out, rumination has developed without a period of previous vomiting (cases of Wirtz, Puoliot). The basis, it seems, is a neuropathic constitution manifesting itself not only in the disturbance of the reflex processes of the automatism of the stomach but also otherwise. Indeed, the presence of various nervous symptoms has been noted by many observers. The psychic factor in my case, namely, the fondness for orange juice and other regurgitated food, suggests itself as a contributory factor.

We know also from observing ruminants that rumination is often enjoyed and that they may regurgitate and ruminate at will, starting the process voluntarily.

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1. Strauch, A.: J. A. M. A. **65**:678 (Aug. 21) 1915.
2. Lust: Monatschr. f. Kinderh. **6**: 1911.
3. Landé: Monatschr. f. Kinderh. **14**:196, 1916.

A perfect dependency of regurgitation and rumination on will and intention I repeatedly observed in a friend of mine, a merchant, aged 37 years, a man of unusual intelligence and learning. He has always enjoyed good health and digestion. He cannot recollect at what age his "peculiarity" started, but he remembers with certainty that when about 20 years old he could voluntarily and easily vomit or regurgitate food, and that often he did rechew and reswallow it. He thought it to be natural until told the contrary by his brother in law, who accidentally discovered his habit about that time. He also remembers that he often astonished his friends by the amount of beer he could drink without intoxication; for he readily would empty his stomach and begin anew to drink, his ability to regurgitate having been kept secret from friends and members of his family. Though ruminating was practiced more or less habitually at the time, at the present it occurs only infrequently, but always voluntarily, more or less consciously and he can easily desist from it, as, for instance, when in society. He would regurgitate and ruminate especially after a very heavy meal, or if he had eaten "food hard to digest," as, for instance, tendinous parts of meat, large pieces of potatoes, swallowed in a hasty meal, lettuce mixed with onions, parts of the stem of lettuce, tough fibers of string beans, the white skin of oranges and the skin of sausage. These parts have "a special irritating influence on his stomach, and cause him a peculiar sensation of fullness but no pain or feeling of pressure." He notices "that the food is indigestible." Under such circumstances, he would rechew and reswallow the regurgitated food but spit out the "indigestible parts, as fibers, etc." and stop regurgitating when no more indigestible particles are felt in the ascending food, or the latter begins to taste sour. He also spits out any desired amount of regurgitated food whenever he thinks "it would be better for him to empty the stomach" or if he fears "the food may not agree with him." He would, after an excessive consumption of coffee during a social evening, out of fear that it would disturb his sleep, regurgitate and spit it out immediately after his arrival at home. Regurgitation is easier with a full stomach than with a partly filled one; therefore, to facilitate it in the latter case, he drinks water or swallows air.

Recently I had the opportunity to observe him after a heavy Sunday dinner at the home of a mutual friend. During almost a whole hour, over and over again, complying with my wish, did he demonstrate his ability to regurgitate and ruminate at will. Probably from mental inhibition due to embarrassment he had to drink water in order to facilitate the first act, but thereafter there was no difficulty in bringing up the food as often as he was asked. A very slight strain with the lower part of the abdomen sinking in and the stomach region bulging

out for a moment, while the glottis is closed, and, as he stated, a kind of "pressing up" is done, sufficed to bring the food up promptly. This was somewhat rechewed and then reswallowed; the fibers of stringbeans and celery and parts of lettuce were spit out. He considers his ability to regurgitate a decided advantage, and attributes to it the preservation of his health during a long stay in the tropics despite his overindulgence in frequent club banquets. It is noteworthy that he never was seasick on his many transoceanic voyages.

Imitation in a number of cases has led to regurgitation (Bruns) and also rumination. Freund and Koerner reported two children, aged 3 and 6 years, respectively, who learned this habit from a ruminant governess, but who were soon cured after her dismissal.

As is well known, stimulation of a certain nervous center by peripheral irritation may inhibit other central functions under ordinary physiologic conditions. The experiments of Pawlow's laboratory demonstrated that a conditional reflex likewise may be inhibited by the introduction of a new stimulus. In a similar manner we succeed occasionally in eliminating the pathologic nervous symptom complex entirely, or in part, by the interpolation of an unwonted factor into the reflectoric motor process, as, for instance, in ruminating or habitually vomiting infants (Meyerhofer,[4] Huldschinsky) by feeding thick gruels. Though some authors believe that gruels lessen regurgitation by irritating the gastric mucosa less or on account of the consistency, Schippers[5] emphasizes the psychic factor of a certain food, as his second patient ruminated every food regardless of its consistency, except bean puree. Likewise, the idiotic ruminant of Landé ruminated gruels but kept down vegetables. Schippers' two patients ceased ruminating as often and as long as they were in the roentgen ray room, so that repeated attempts to study the process of rumination roentgenologically failed, it having been impossible to accustom the babies to the room.

Scolding and threatening may stop rumination at least for a short time. We act on a similar physiopsychologic principle if we introduce therapeutically diversion by sounds, play, swinging, change of surroundings as an inhibitory factor and succeed in making the ruminant baby or child desist from his pathologic habit. The less established and inveterate the pathologic mechanism is, the more prompt, ceteris paribus, will be the inhibitory and curative effect of the former upon the latter. This may explain the prompt therapeutic result in my case.

Wirtz and later Goett[6] and Landé observed the beneficial effect

4. Meyerhofer: Therap. Monatschr., April, 1912, p. 262.
5. Schippers: Ztschr. f. Kinderh. **10**:92, 1914.
6. Goett: Ztschr. f. Kinderh. **16**:177, 1917.

of distracting play, and Bruening [7] noticed a child almost immediately cease ruminating when a change of surroundings was effected by giving the patient into individual care. In a case of Somersalo [8] nibbling or sucking a piece of zwieback after meals made the child, who also was given gruels, forget his rumination habit by distraction. However, there are a number of cases that resisted the most varied dietary and intentional or unintentional psychic therapy.

Landé [3] considers rumination in certain cases as "cage disease," long stay in a hospital without diversion and entertainment, the ennui of isolation occasionally creating the affection in her view. Transfer of the patient among lively children, etc., may prove effective therapeutically.

It has long been known that in some adults diversion by animating conversation after meals inhibits rumination and its first phase, the regurgitation and that they may be able to suppress it voluntarily (autosuppression, Boas) the psychic factor of discipline being by all means the principal therapeutic agent. Ylppoe,[9] in whose opinion rumination in infants is often a consequence of aerophagia and its accompanying regurgitation, places the baby on its abdomen in order to prevent air-swallowing during nursing, which position by distraction exerts a psychogenic therapeutic effect. In ruminants that soon became used to this new position and again began to ruminate, the necessary distraction was obtained by placing the children in the abdominal posture on a mobile suspension. The results were excellent, and the author recommends this method also in treating habitual vomiting.

In a ruminating girl, 5 months old, as reported by me, artificial obstruction of the nose by insertion of cotton after each meal while the baby was kept lying down on her back, interfered with rumination and caused discomfort so that she almost entirely ceased even attempting to ruminate, though various methods had previously been employed unsuccessfully. The regurgitation subsided gradually and ceased practically within two weeks. I was led to the systematic use of this "heroic" procedure by the observation that regularly, as often as the nose was pinched, experimenti causa, and nasal respiration thus obstructed, while the baby was kept lying on her back she at once resentfully stopped ruminating and swallowed the food in order to get air through the mouth. One could not help thinking that the child desisted from rumination eventually because of discomfort and urgency of air-hunger entailed by the act, and that after a sufficient

7. Bruening: Arch. f. Kinderh. **60**:116, 1913.
8. Somersalo: Arch. f. Verdauungskrankh. **16**:167, 1920.
9. Ylppoe: Therap. Halbmonatschr. **34**:76, 1920.

time regurgitation itself was given up, because it could no more lead to the pleasurable act of rumination at ease. Unfortunately, soon the baby contracted measles during a ward epidemic and died from complicating bronchopneumonia.

To obtain satisfactory results one must not forget that with nose obstruction solid or semisolid food brought up into the mouth would not to the same degree interfere with mouth breathing and be distressing in the upright posture during the act of rumination as would milk that fills up the mouth of a baby lying on its back.

In attacking therapeutically the last link in the chain of the motor complex, also the preceding links were being eliminated. The "logic" of this procedure is proven not only by the immediate results of repeated experimental nose obstruction and the eventual therapeutic success in my case, but is evident also to those who keep in mind the similar principle underlying the successful curative administration of bitter pills during meals in some adults, the intense bitterness of the drug in the regurgitated food inducing them to cease not only ruminating but also its first phase, namely, regurgitating.

In merycism in babies, associated with severe pylorospasm or a marked motor insufficiency with stagnation and fermentation or with organic disturbances, such as dilatation of the cardia or the lower part of the esophagus, neither psychic diversion nor nose obstruction will abolish the vomiting or regurgitation (the first and essential phase of merycism); in so far as it depends on these lesions it will still continue. The urgency of the organic component is simply beyond the reach of a psychic influence. Here the therapy naturally must first be aimed at these organic lesions or other anomalies. In the adult ready cures of rumination have repeatedly followed the cure of associated gastro-intestinal diseases.

In connection with the observations as to the rôle the psyche may play in the inhibition of rumination and regurgitation, I wish to submit the following highly interesting observation of a complete cessation of this affection during pertussis and a subsequent cure (from my private practice).

CASE 2.—*History.*—James Q., born Oct. 3, 1917, was a very nervous, irritable, stubborn, but physically well developed boy. Both parents are likewise very nervous and his three sisters had suffered from enuresis nocturna. At the age of 1 year (middle of October, 1918) he suffered from influenza with pneumonia and has often since that time had convulsions, which under bromin therapy became finally less frequent. For a period bromin was discontinued on account of symptoms of intoxication.

In May, 1919, the boy began frequently to "spit up" his food. Whether this was due to large dosages of bromin or not cannot be decided with certainty, as I rarely saw the boy during this period. In August, 1919, I found that he ruminated; the exact beginning of the act could not be determined. After almost every meal, even small ones, the boy would bring up the ingested

food; liquids, such as milk, were borne much better, and if brought up, were reswallowed immediately; semisolid or solid foods were reswallowed after a few masticatory movements.

The rumination was kept up in frequent repetitions and much enjoyed. During some periods conditions would improve, and there was one week when he did not ruminate at all; however, during other periods the trouble would be aggravated and he would ruminate for two or more hours after each meal, even shortly before the next one and practically the whole day during his play with other children. This happened especially during the day previous to an epileptic seizure, when he was very irritable, and during constipation. There was for a long time a very rancid odor to the regurgitated food. Only rarely a real vomiting of any violence occurred; but whenever food would spill over, for instance on the highchair, the boy would put it back into his mouth with his fingers or the spoon and re-eat it despite its rancidity. If scolded he would stop ruminating for a moment, resentfully run away and recommence ruminating.

Treatment.—Various quantitative and qualitative changes of diet, long and short intervals, magnesium, etc., failed to have any noticeable effect. The nervous tension of the home life, through lack of cooperation, rendered pedagogic therapy futile. In April, 1920 the boy contracted pertussis together with the other children of the family. He suffered the most. The paroxysms were very frequent, violent and accompanied by vomiting that continued to the end of May. His general condition, however, was little affected thereby. The remarkable feature was that the boy during this illness had entirely ceased ruminating. Only on May 9 and 19 did he ruminate a very little after breakfast and again in the last week of May and the first week of June. His mother volunteered the remark, "he tried, but did not know how to do it any more." Since that time no more rumination has occurred.

The assumption that rumination should have stopped from lack of stomach contents on account of frequent vomiting is, of course, not tenable, especially in the presence of the fact that the boy's physical condition was good, no signs of underfeeding existing. Most probably it was the mechanical interference with easy and comfortable rumination by the violence of real vomiting and expectoration during the paroxysms, together with his own and his sister's suffering, and the fear of new attacks becoming the center of his attention (as it was so with his worried parents) that crowded out the former neurotic manifestation with the same psychic force as an "event" occasionally has done in adult ruminants. This case is the more noteworthy, since pertussis has been observed to have led to rumination, evidently by the accompanying vomiting.

A similar observation of a curative effect of an intercurrent disease on rumination has been published by Wanietschek.[10] The boy ruminated from the second month of life unceasingly and resisted various treatments, until a temporary cessation took place in his seventh year due to adenectomy. In his eighth year of life a complete and permanent cure occurred in connection with a transitory postdiphtheritic deglutition paralysis. The author ascribes this cure to autosuggestion, maintaining that the boy, much troubled by the disturbance of the

10. Wanietschek: Jahrb. f. Kinderh. **82**:66, 1915.

pharynx (deglutition mechanism), had to avoid the regurgitation of food as much as possible. Schippers observed rumination in two babies to cease temporarily during dyspepsia with meteorism.

That nervous habits may be given up during an illness which is accompanied by malaise, is well known. I have only lately seen in my Cook County Hospital service a 12 months old head roller completely cease this stereotypia during measles. Whether this was permanent, I did not ascertain, as the child left my observation too early, having been transferred to the Contagious Hospital.

A CASE OF ACUTE LEUKEMIA IN AN INFANT*

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The case of acute leukemia herewith reported, occurring apparently at birth or very shortly thereafter, is, as far as I have been able to discover in the literature, unique in that the patient is the youngest person in whom this disease has been noted. However, Tancré [1] within the past year reported a case in an infant in which the disease began at the age of one month and terminated fatally three months later. Holsclaw [2] also outlines the findings in an acute lymphatic leukemia in a baby, aged 11 months.

The history of the case under discussion was obtained from the family physician, Dr. Marie Knudson, of Boston. It is through her courtesy that the case is being presented.

REPORT OF CASE

The patient is a male baby, 6 weeks of age.

Family History.—The father and mother (both born in Italy) are living and well. Three other children are living and well. The mother has had no miscarriages. There is no known family history of tuberculosis, syphilis, renal or blood disease.

Past History.—The baby was full term and normally delivered. It was breast fed until its present illness. Its birth weight was about nine pounds. There has been no history of infection.

Present Illness.—The baby when about 3 weeks old began to have marked difficulty with its feeding—vomiting most of its food, passing from five to seven loose greenish stools each day, and losing weight. This had been present for about a week and was becoming more severe. The diagnosis of improper feeding with indigestion was made, and its diet regulated by giving alternate feedings of a modified milk formula together with breast milk. The baby did not seem to improve after various attempts to find a satisfactory formula. This led to a more careful physical examination of the baby, and an enlarged axillary lymph node was noted. This lymph node, according to the mother, had been present since birth and had been slowly increasing in size until at nearly 6 weeks of age it had become as large as a walnut. A greatly enlarged spleen was also found at this time. These observations of Dr. Knudson's, in addition to a rather obvious anema, led her to examine the blood and to refer the case to Dr. H. I. Bowditch of the Children's Hospital Staff. Through his kindness I was permitted to see the patient and to report on the blood findings.

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* From the Departments of Pathology, Medicine, and Pediatrics of the Harvard Medical School.

* This is Study 14 of a series of studies in the Physiology and Pathology of the Blood from the Harvard Medical School and allied hospitals.

1. Tancré, E.: Acute Lymphatic Leukemia in Infants, Arch. f. Kinderh. **67**:7, 1918.

2. Holsclaw, F.: Case of Acute Lymphatic Leukemia, with Autopsy Report, Arch. Pediat. **35**:151 (March) 1918.

Physical Examination.—The baby was a pale, fairly well developed, but poorly nourished infant, about 6 weeks of age, lying in bed, crying fretfully. The child appeared to be ill, was pallid, with a peculiar grayish yellow hue to the skin. The mucous membranes were pale. The sclerae were white, practically bloodless. The pupils were equal and reacted to light. The nose and throat were negative. There were ten or twelve purpuric spots scattered over the body and under the left axilla. These varied in size from a pinhead to about the size of a silver half dollar. The chest was essentially normal in development. The lungs were not abnormal. The heart was not enlarged. There was a loud systolic murmur best heard over the pulmonic area which was considered functional. The abdomen was asymmetrical, protruding prominently on the left side from below and to the right of the umbilicus to the costal margin. On palpation the spleen was felt filling two thirds of the abdomen. There was a prominent notch. The spleen was very firm and had a rounded edge. The liver was slightly enlarged, palpable a finger's breadth below the costal margin. There was a slight enlargement of all the lymph nodes. In the left axilla there was one large discrete nodule, the size of a large walnut, firm and freely movable under the skin. This was apparently not tender and showed no evidence of inflammation. It interfered slightly with adduction of that arm. The reflexes were all normal.

BLOOD EXAMINATION

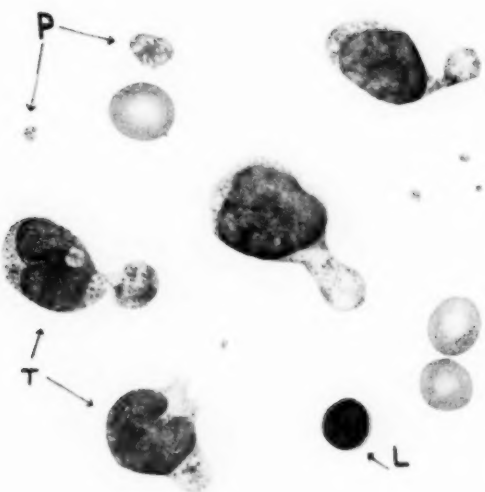
	Age		
	6 Weeks	7 Weeks	8 Weeks
Leukocytes	189,000	201,000	30,000
Polymorphonuclear leukocytes	1%	2%	2%
Pathologic lymphocytes (large)	22%	18%	32%
Pathologic lymphocytes (small)	69%	72%	63%
Normal small lymphocytes (?)	6%	7%	2%
Large mononuclears (?)	2%	1%	1%
Erythrocytes	2,624,000	1,440,000	900,000
Achromia	++	++	+++
Anisocytosis	+	++	++
Poikilocytosis	+	++	++
Polychromatophilia	0	+	+
Stippling	0	0	0
Platelets	Definitely diminished	Definitely diminished	Markedly diminished

Subsequent History.—During the two weeks' period before death that he was under observation, the baby's condition became progressively worse and he continued to lose weight steadily. The spleen became larger, occupying practically the entire abdomen. The axillary lymph node at the time of death was the size of a large hen's egg. Fever developed and remained constantly high. At the age of 2 months, the baby developed a terminal pneumonia and died very suddenly. No necropsy could be obtained, which is regretted, for much of the uncertainty regarding the rather unusual cells found in the blood might have been cleared up by a microscopic examination of the spleen and bone marrow.

The presence of the axillary lymph node from birth suggests a prenatal development of the disease. It is interesting to note in this connection that the mother's blood picture and white cell count was definitely normal.

DISCUSSION

The chief point of interest is the character of the lymphocytes. These cells vary greatly in size and are practically all pathologic cells. A few comparatively normal small lymphocytes occur Stained by



(L.) Normal small lymphocyte. (T.) Large pathologic lymphoid "tumor" cells, showing characteristically the intense granulation of both the nuclei and the cytoplasm and the "budding" of the cytoplasm into long pseudopodia which break off and can be seen floating free in the peripheral blood stream as (P.) pseudoplatelets which are with difficulty differentiated from normal platelets.

Illustrating Article by Lawrence Weld Smith, M.D.
American Journal of Diseases of Children, February, 1921

Wright's method all the larger lymphocytes are exceedingly granular in character, their cytoplasm being filled with small, slightly basic staining granules which almost conceal the cytoplasm itself. This is true of the smaller form of cell, also, but is less noticeable. That they belonged to the lymphoid and not the myeloid series was for some time very uncertain, but by using Goodpasture's modification of Graham's oxidase stain, their lymphoid character was definitely determined. This was because the granules failed to be colored by the oxidase stain as they characteristically do in cells of bone marrow origin, except megakaryocytes. These large pathologic lymphoid "tumor" cells resemble somewhat megakaryocytes and though conceivably the cells in this case might be pathologically megakaryocytes, it is believed that such is not the case.

Another feature of these large pathologic lymphoid "tumor" cells is the presence of apparent pseudopods. These can be seen budding from the cytoplasm in many instances, becoming pinched off, and thrown into the blood stream, forming what we may for lack of a better term call "pseudoplatelets." These pseudopodia may be elongated with multiple points of what seem to be division. With Wright's stain these small bits of protoplasm are almost indistinguishable from platelets, for they collect acid staining granules in the center of each process which are in no way associated with the cell nucleus as is shown in the accompanying illustration.

Using the vital staining method with brilliant cresyl blue Minot has noted that "pseudoplatelets" can be distinguished from the typical true platelet, by the absence of the so-called "apron" of the latter. The "pseudoplatelets" as a rule, are much more sharply defined peripherally than are the true platelets, but the staining has to be extremely accurate to show these slight differences. By ordinary fixed staining methods the two are practically indistinguishable, and the appearance of the "pseudoplatelets" tempts one to conceive that possibly the platelets may, under certain abnormal conditions, be formed by other cells than the megakaryocyte of the bone marrow.

These pseudopodia are found almost entirely budding from the larger lymphocytes. They occur in approximately 20 per cent. of these cells and usually as a single process, although they may be multiple with as many as ten or twelve smaller processes. Occasionally, a single "bud" may be pinched off in two or more places. Again, this is unusual. On counting one hundred white cells differentially, usually five or six of these "budding" cells are seen, and approximately a dozen or fifteen of these free circulating "pseudoplatelets."

Dr. George R. Minot, in discussing the blood findings of this patient, commented on the fact that in a much less marked degree,

however, he had noted this "budding" in atypical lymphoid cells, immature large mononuclear cells and endothelial phagocytes present in certain pathologic bloods. From his work with cresyl blue preparations, he too, remarks on the similarity of the true platelet and these "pseudoplatelets."

Such a case as this offers much of speculative interest, but it is not my purpose at this time to do more than record the observations made and to leave the reader to draw his own deductions.

SUMMARY

A case of lymphatic leukemia in an infant is reported. According to the history, the disease began definitely at the age of 3 weeks, while the evidence seems to suggest strongly an intrauterine development of the condition.

The lymphocytes are nearly all of a pathologic type. They show an excessive granulation of the cytoplasm, making a differential diagnosis from myelogenous leukemia extremely difficult. They further show to a marked degree another unusual feature, namely, a budding of the protoplasm. Some of these buds become detached and circulate in the blood. They very closely resemble normal true platelets.

I wish to take this opportunity to thank Miss E. Piotti for her invaluable assistance in preparing the plate which accompanies this report.

BROMIN POISONING THROUGH MOTHER'S MILK*

FRANK VAN DER BOGERT, M.D.
SCHENECTADY, N. Y.

REPORT OF CASE

History.—A 6 months old nursing baby was referred to Dr. Hartman of Alexandria Bay to the pediatric department of the diagnostic clinic of the state department of health at Carthage, N. Y., Oct. 1, 1920.

The infant presented a seemingly painful papulopustular eruption, the lesions being grouped and each group surrounded by a clear cut inflammatory area. The lesions were distributed principally on the arms, lower legs and buttocks, and were just beginning to show on the face and scalp. Several patches had assumed a more red or purplish-red color, had reached a papillomatous or condylomatous condition and covered much skin surface, one on the lower leg being at least one square inch in area. There was a history of a general "white" rash at birth, followed by the present eruption at 6 weeks of age. A marked rattle had been heard in the throat, dating from soon after birth, but there was no history of "snuffles." Some irritation of the nasolabial fold was noted at the time of examination.

Family History.—The mother is exceedingly nervous, and for this condition has been taking for the past two years a proprietary remedy known as Miles' Restorative Nervine. The 1912 report of the Massachusetts Board of Health describes this preparation as bromids in sugar syrup with benzoic acid—a heavy syrup containing about 17 per cent. bromids, chiefly potassium and sodium, with a smaller amount of ammonium bromid and a small amount of benzoic acid. The analysis made by the American Medical Association, reported Sept. 9, 1916, is as follows:

MILES' RESTORATIVE NERVINE

	Per Cent.
Ammonium bromid	1.13
Potassium bromid	9.87
Sodium bromid	6.93
Sodium chlorid	0.24
Benzoic soda, etc.	

The baby had been given no medication until two days before appearance at the clinic, when some small sedative tablets were prescribed by the attending physician.

Diagnosis.—The diagnosis of bromid eruption was made by Dr. Edward H. Marsh, dermatologist in attendance, before the history of the mother's medication had been obtained. A specimen of the breast milk was secured later, and an analysis by Prof. Edward Ellery of the department of chemistry of Union College showed it to contain bromin in more than traces. The small amount of breast milk obtainable was probably responsible for the small amount of bromin demonstrated.

COMMENT

Instances of the elimination of drugs through the milk of the nursing mother occur in literature. Holt[1] says that the elimination

* Received for publication Oct. 20, 1920.

1. Holt, L. E.: Diseases of Infancy and Childhood, Philadelphia, D. Appleton & Company, 1916, p. 143.

of drugs through the milk is somewhat uncertain and variable. "Few of those popularly supposed to affect the child through the milk really do so." He says that belladonna given in full doses regularly appears in the milk, that the iodids and bromids when long administered may be eliminated in sufficient quantity to produce their constitutional effects on the child.

Dunn [2] believes that the fact that certain drugs taken by the mother can be excreted by the milk has been definitely proven and quotes Talbot, in whose list bromid appears. He says, however, that these drugs are found in the milk only in slight traces and can probably do no harm, except in the case of salvarsan, when sudden death of the infant has occurred after treatment of the mother.

Chapin and Pisek [3] advise that great care be exercised in giving drugs to nursing women, as they may be excreted in the milk. They do not specifically mention the bromids.

Budin [4] apparently does not mention drugs but reports a case of convulsions in an infant suckling a mother who was taking large quantities of alcoholic beverages. The patient was quickly cured when a wetnurse was substituted.

Louis Fischer [5] includes bromids in his list, and states that physiologic experiments have frequently demonstrated the fact that many drugs can be given to the infant through the milk.

Still [6] warns that a possibility always to be remembered where the breast milk appears to be disagreeing with an infant is that the mother may be taking some drug which is either excreted in the milk or affects the milk indirectly.

Koplik [7] mentions only iodin, salicylic acid and atropin as being eliminated in the milk, but says very little is actually known as to the appearance of drugs.

Grulee [8] believes that, in general, one may say that in physiologic doses very few drugs pass over into the breast milk, while in poisonous doses most of them do.

According to Griffith [9] bromin passes into the milk to some extent and occasionally in a way to affect the infant seriously.

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2. Dunn, C. H.: Pediatrics **1**:249, 1917.
3. Chapin and Pisek: Diseases of Infancy and Childhood, New York, William Wood & Co., 1913, p. 122.
4. Budin, P.: The Nursling, 1907, p. 93.
5. Fischer, L.: Diseases of Infancy and Childhood, 1914, p. 88.
6. Still, G. F.: Common Disorders and Diseases of Childhood, London, Oxford University Press, 1910, p. 26.
7. Koplik, H.: The Diseases of Infancy and Childhood, Philadelphia, J. B. Lippincott Company, 1910, p. 97.
8. Grulee, C. G.: Infant Feeding, Philadelphia, W. B. Saunders Company, 1914, p. 79.
9. Griffith, J. P. C.: The Diseases of Infants and Children, 1919, p. 106.

Lowenburg [10] does not mention bromids.

I have been unable to find a specific instance relating to the bromids, although Talbot [11] refers to Burcura as his authority. This reference I have not obtained.

Reed [12] has collected a large number of cases in which nursing babies have been apparently affected by drugs administered to the mother. He refers to Rosenhaupt, who used potassium and sodium bromid in an epileptic woman, and was able to demonstrate chemically that the bromin passed over into the milk. He does not consider this dangerous, however, nor especially to be avoided, since only an infinitesimal amount passes over. He says that the transmission of medical substances through the milk of the mother to the babe is a subject of more than usual obscurity, and that owing to the prevalence of tradition and the absence of thorough and accurate methods in collecting the data, the observations are for the most part valueless.

CONCLUSION

In conclusion, it might be added that the papillomatous or condylomaform areas are described by Stelwagon [13] as a rather rare manifestation occurring especially in children and adolescents, and that, especially in children, the eruption may persist for several weeks after the drug has been discontinued. This is apparently more apt to occur in the condylomaform type.

Fox [14] speaks of the treatment of drug eruption as a simple matter, but excepts a few cases of bromid eruptions which do not disappear speedily.

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10. Lowenburg, H.: Infant Feeding and Allied Topics, Philadelphia, F. A. Davis Company, 1916, p. 43.
11. Morse and Talbot: Diseases of Nutrition and Infant Feeding, New York, The Macmillan Company, 1915, p. 114.
12. Reed, C. B.: Surg., Gynec. & Obst. **6**:514, 1908.
13. Stelwagon, H. W.: Diseases of the Skin, Philadelphia, W. B. Saunders Company, 1902, p. 424.
14. Fox, H. F.: Atlas of Diseases of the Skin **1**:59, 1905.

A STUDY OF SEVENTY-THREE CASES OF ACUTE ARTHRITIS IN INFANTS*

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The invasion of the joints and periarticular tissues by pyogenic organisms in infants is by no means a rare condition. The inflammation of the joint is usually secondary to an infection of the epiphysis. However, in many instances the inflammation spreads from the epiphysis to the periarticular tissues without affecting the joints proper. Clinically, there is great swelling, with or without suppuration, tenderness, redness and a great amount of induration.

This paper is a statistical study of seventy-three consecutive cases admitted to the Babies Hospital in the past fifteen years. The common conception seems to be, that purulent arthritis always follows a focal lesion. This may be true, but the focus of infection is indeterminable in the majority of instances. Of the seventy-three patients reported in this study, only thirty-two gave a history or showed on examination when admitted, any definite source of infection. Many are included in this number who had had pneumonia or some other acute illness several weeks previously and the relation between the original infection and the arthritis is not at all clear. For instance, following a pneumonia, an infant may develop a streptococcic arthritis.

Table 1 gives the possible sources of infection in these thirty-two infants.

To illustrate the difficulties in drawing conclusions as to the possible source of infection, the ten cases preceded by pneumonia were analyzed. Only three of these showed pneumococci in the pus aspirated from the lesions; one showed the gonococcus, one the aurococcus and one the influenza bacillus while four failed to show any bacteria in the aspirated material.

The number of males seems to predominate. There were forty-six boys and twenty-seven girls. This difference may, in part, be due to the large number of girls rejected on admission on account of positive vaginal smears. The rule in the hospital has always been to reject all children suspected of having any gonococcic infection of the genitals. However, the greater number of boys affected would seem to indicate that vaginitis is not as common a cause of arthritis in infants as is usually supposed.

The ages of these infants is an interesting study.

* Received for publication, Aug. 30, 1920.

TABLE 1.—Sources of Infection

Infection	No. of Cases
Pneumonia	10
Navel infection	4
Furunculosis	3
Cerebralspinal meningitis	2
Cervical adenitis	2
Vaginitis	2
Ophthalmia	2
Infected wounds	2
Otitis media	1
Scarlet fever	1
Breast abscess in mother	1

TABLE 2.—Ages of Patients

Age	Number of Cases
0 to 1 month	12
1 to 2 months	4
2 to 3 months	9
3 to 4 months	3
4 to 5 months	8
5 to 6 months	3
	39
6 to 7 months	6
7 to 8 months	5
8 to 9 months	4
9 to 12 months	0
	15
12 to 15 months	7
15 to 18 months	4
	11
18 to 21 months	4
21 to 24 months	0
	4
24 to 30 months	1
30 to 36 months	1
36 months	2

TABLE 3.—Order of Frequency in which Joints were Affected

Joint	Number
Knee	27
Ankle	26
Wrist	25
Shoulder	24
Hip	17
Elbow	14
Metacarpophalangeal	12
Thumb	3
Interphalangeal	9
Hand	8
Foot	1
Sternoclavicular	6
Metatarsophalangeal	5
Great toe	3
Temporomandibular	2
Intercarpal	2
Carpometacarpal	1
Tarsometatarsal	1
Intertarsal	1

TABLE 4.—MICROORGANISMS CAUSING THE INFECTION

Streptococcus	18 cases
Pneumococcus	14 cases
Gonococcus	7 cases
Staphylococcus	3 cases
Influenza	3 cases
Colon bacillus	1 case
Meningococcus	1 case

TABLE 5.—RELATIONSHIP BETWEEN ORGANISM AND NUMBER OF JOINTS INFECTED

Organism	Number of Cases
Streptococcus affected one joint in	4 cases
Streptococcus affected two joints in	2 cases
Streptococcus affected three or more in	12 cases
Pneumococcus affected one joint in	9 cases
Pneumococcus affected two joints in	4 cases
Pneumococcus affected three or more in	1 case
Gonococcus affected one joint in	1 case
Gonococcus affected two joints in	1 case
Gonococcus affected three or more in	5 cases
Influenza bacillus affected one joint in	2 cases
Influenza bacillus affected two joints in	0 cases
Influenza bacillus affected three or more in	1 case
Staphylococcus affected one joint in	1 case
Staphylococcus affected two joints in	1 case
Staphylococcus affected three or more in	1 case

TABLE 6.—NUMBER OF JOINTS INVOLVED IN INDIVIDUAL CASES AND CAUSATIVE ORGANISM

Number of Joints Affected	Number of Cases	Organism
8	1	Gonococcus
7	1	Streptococcus
6	2	1 Streptococcus 1 Pneumococcus
5	4	2 Streptococcus 2 Gonococcus
4	4	3 Streptococcus 1 Gonococcus
3	8	5 Streptococcus 1 Gonococcus 1 Influenza

TABLE 7.—RESULTS OF BLOOD CULTURE STUDIES

	Organisms of Joints					
Blood Cultures	Streptococcus	Gonococcus	Staphylococcus	Influenza Bacillus	Pneumococcus	None
10 negative	0	1	1	0	4	4
9 positive	4	0	0	1	2	2

TABLE 8.—CAUSES OF DEATH

Diseases	Cases
Bronchopneumonia	15
Marasmus	13
Erysipelas	5
Meningitis	4
Peritonitis	2

If the number of babies are arranged in six month periods, the result is striking in showing that the younger the infant, the greater seems to be his susceptibility to purulent arthritis. Fifty-three per cent. of all the babies in the study were under 6 months of age, and 74 per cent. were under 1 year. The twelve babies who were one month or under, were probably victims of birth infection. This, however, is difficult to substantiate for only four infants presented definite signs of ophthalmitis on admission. Other routes of infection than the cord are responsible. It is possible that bacteria enter the blood stream through injuries to the mucous membranes of the mouth or to trauma from forceps.

Forty-two per cent. of the children had only one joint affected; 25 per cent. had two joints affected while 33 per cent. had more than two joints affected. The largest number of joints affected in any one case was eight. In Table 3 the joints affected are arranged according to frequency.

Table 3 also shows 95½ per cent. of the joints affected were in the extremities.

In forty-seven babies the organism responsible for the infection was isolated and identified by culture. Table 4 shows that the principal organisms were the streptococcus and the pneumococcus.

To ascertain whether an organism is more prone to attack one or more joints, Table 5 was compiled.

It would seem that the streptococcus and gonococcus are much more prone to affect multiple joints while the pneumococcus seems to be limited more often to one or two joints. This bears out the usual impressions.

From the sterno-clavicular joint the streptococcus was isolated in two children, the gonococcus in two and the influenza bacillus in one child. Gonococcus and streptococcus were found in one case in which the temporomandibular joint was affected. One baby had eight joints affected in the course of the disease. This was the largest number in any one child in the series and the gonococcus was responsible. Another child had seven joints affected in which the streptococcus was isolated from all.

During the past two years blood cultures have been made routinely in all cases of arthritis. There have been nineteen children in whom one or more blood cultures have been taken. In ten, the culture proved sterile. Of the nine who showed a positive growth, four proved to have streptococcus, three pneumococcus, one the influenza bacillus and one staphylococcus.

Two children had positive blood cultures but showed no organisms from the joints. One had a positive culture of staphylococcus and the other a mixed infection of pneumococcus and meningococcus. All

the children who had a streptococcus in the joints had also a positive blood culture for the same organism. Forty per cent. of the negative blood cultures were in children who showed no organisms in the joints while in the positive cultures only 22 per cent. had no organisms in the lesions. In other words, when organisms are found in the joints there is more apt to be a positive blood culture. In no case was a different organism found in the blood than was isolated from the arthritic lesion. The series seems too small, however, to draw any very definite conclusions.

The prognosis is not very hopeful among infants with this disease. Fifty-three per cent. died in the hospital and 9 per cent. were discharged unimproved, which usually means that the children were taken out of the hospital against the advice of the physicians. Thirty-eight per cent. were followed and reported entirely well or greatly improved.

Table 9 gives the number of children and the mortality in each age group.

TABLE 9.—MORTALITY OF VARIOUS AGE GROUPS

Age	Number of Cases	Died	Mor ality Percentage
1 to 6 months	39	25	64.1
6 to 12 months	15	8	53.3
12 to 18 months	11	4	36.2
18 to 24 months	4	1	20.0
24 to 30 months	1	1	100.0
30 to 36 months	1	0	
36 months	2	0	

Five children of this series have recently been seen, 2 eleven years, 1 eight years, 1 six years and 1 four years after discharge from the hospital. The functional result in all is perfect. One child when admitted to the hospital in 1911, at 5 months of age, was suffering from a severe infection of the right hip. Three large incisions were made with drains inserted through and through from beneath Poupart's ligament to the gluteal region. The infecting organism was the streptococcus. The result was perfect, except for a very slight limp. The thigh can be moved normally in every direction. There is no appreciable difference in the length of the extremities. Very few of these children died from the disease itself. In the cases that came to necropsy, evidence of some other disease sufficient to cause death was found. The other children either died from diseases determined clinically or from slow wasting. The causes of death recorded in the histories are shown in Table 8.

As would be expected, four of the children who died of erysipelas were infected in their joints with streptococcus.

In one of the children with meningitis, the influenza bacillus was recovered from the joints and spinal fluid. Another child had the influenza bacillus in the spinal fluid, blood and joints. A third child had streptococcus in blood, spinal fluid and joints. The fourth died suddenly and unfortunately no examination is recorded of the spinal fluid. The material aspirated from the baby's joints was sterile.

The prognosis is affected materially by the age. The older the baby, the better chance he has to recover. The high mortality among young babies is due in great part to the difficulty of feeding.

I am indebted to Dr. L. Emmett Holt, physician in chief to the Babies' Hospital, for the privilege to report these records.

DEVIATION OF THE AORTIC SEPTUM: COMPLETE TRANSPOSITION OF THE GREAT VESSELS, WITH REPORT OF TWO CASES IN INFANTS*

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Congenital cardiac abnormalities are encountered sufficiently often to emphasize the manifold possibilities of such defective development, their frequent multiplicity of expression in a single case, and the difficulties in the way of recognizing antemortem the actual lesions present. Such signs as cyanosis since birth, a loud murmur and thrill at the base of the heart, and clubbed fingers—when taken together are quite pathognomonic of congenital heart disease. But defects of the organ acquired in utero are seldom single, and the mechanical explanation of the physical findings is often a difficult problem.

Complete transposition of the great vessels is uncommon enough to warrant publication of such cases as are proved at necropsy. I have found two instances of this condition in infants, one living three weeks and the other twelve months, the duration of life and the relation of the heart lesions thereto furnishing an instructive feature. The cases are from the clinic of Dr. Chas. Hunter Dunn at the Infant's Hospital, Boston, and I am indebted to him for the clinical data.

REPORT OF CASES

CASE 1.—Male, white, aged 12 months.

Family History.—Father and mother are living and well. There is no history of miscarriages, tuberculosis or syphilis.

Past History.—Born at full term, normal delivery, weighing 5½ pounds. Cried normally but was blue. He has had an occasional cold.

Present Illness.—Baby has been blue since birth, especially when he cries. He is sent in with a diagnosis of congenital heart disease and for regulation of his feeding.

Physical Examination.—Baby is cyanotic, more so on crying. Anterior fontanel admits two fingers. Craniotabes present. There is right interscapular dulness and spinal dulness to the level of the fourth vertebra. Heart: There is a palpable thrill and diffuse impulse over the precordium. Enlargement is made out 2 cm. outside the left nipple line, and 3 cm. from the midsternal line to the right. A systolic murmur is heard at the apex and faintly in the vessels of the neck

A week later the following note was made: "There is still marked cyanosis which is increased by crying. The cardiac impulse is diffuse and there is a

* Received for publication Sept. 23, 1920.

palpable thrill. The heart borders are unchanged. A loud systolic murmur is heard all over the precordium, transmitted into the left axilla and back but not into the vessels of the neck."

Diagnosis.—Pulmonic stenosis and patent interventricular septum.

Pulse rate varied between 135 and 170 per minute and respirations from 37 to 78. The following week he developed a fever and chest signs of bronchopneumonia and died.

Necropsy Diagnoses.—Complete transposition of aorta and pulmonary artery; patent foramen ovale; patent interventricular septum; vegetative endocarditis of the wall of the septum defect; vegetative endocarditis of the tricuspid valve with insufficiency; right auricular and ventricular hypertrophy; passive congestion of the lungs.

Fig. 1.—Case 1. Heart, anterior aspect. 1. Aorta. 2. Pulmonary artery. 3. Ductus arteriosus.

Body is that of a somewhat emaciated male white infant, 60 cm. in length. There is slight postmortem lividity. The primary teeth are present. There are no external stigmata and no clubbing of the fingers.

Peritoneal Cavity: The abdominal viscera are in normal positions. The urachus is closed.

Pleural Cavity: Contains no free fluid.

Mediastinum: The thymus is small and of loose texture, weighing about 4 gm. The greater part of the mediastinum is occupied by the enlarged heart which lies in about normal position.

Pericardial Cavity: Contains about 10 c.c. of clear fluid.

Heart: Weight, 76 gm.; diameters, 8.5 by 7 cm. Several abnormalities are apparent on opening the pericardium. It is considerably enlarged, the right

auricle markedly dilated and placed rather posteriorly. The general contour of the organ follows about normal lines, although the anteroposterior diameter is probably increased out of proportion to the general hypertrophy. Viewed anteriorly, the most conspicuous anomaly is the origin of the aorta, this vessel arising from the conus arteriosus of the right ventricle a little to the right of the usual origin of the pulmonary artery.

The pulmonary artery has its origin in the left ventricle, whence it arises to the left of and slightly posteriorly to the aorta, the greater part of the arch of which is in close apposition to the convexity of the pulmonary artery. The left auricle is small and empty, but its appendage is rather elongated, extending about 0.5 cm. along the anterior longitudinal sulcus.

The superior and inferior venae cavae enter the dilated right auricle, their ostia being 1 cm. apart, and that of the inferior vessel being high up on the posterior wall.

The aorta is 1.3 cm. in diameter at its base. It gives off two main coronary branches, the right and left, the left making its exit in plain view anterior to the pulmonary artery, passing under the left auricular appendage where it gives off its auricular and anterior circumflex branches. From the aorta arise in a normal manner the innominate, left common carotid and left subclavian arteries. The ductus arteriosus is 1 by 0.3 cm. and connects the pulmonary artery at a point on the upper anterior wall just proximal to its primary division, to the aorta just below the origin of the left subclavian artery. It is entirely closed by an endarteritis.

The incision through the tricuspid valve and lateral wall of the right ventricle encounters a greatly hypertrophied myocardium. That of the right auricle is hypertrophied in proportion. The foramen ovale is widely open, the patency being 1.2 cm. in diameter, practically round in outline and bordered by a rather high limbus. The tricuspid valve leaflets are nodular and thickened, pale ragged vegetations covering the free borders and producing sufficient puckering to cause a high degree of insufficiency. The circumference of the valve orifice is 4.7 cm. The chordae tendineae are taut and the papillary muscles greatly hypertrophied.

In the membranous portion of the interventricular septum is a defect 0.8 cm. wide and rounded in outline. The greater part is occluded by a mass of cauliflower-like granulations so that an actual opening of only 0.8 cm. exists along the lower border.

The left auricle is small and its wall is only 0.1 cm. thick (after fixation). The mitral valve is normal. The left ventricle wall is only 0.4 cm. thick. From the left ventricle 1 cm. above and to the left of the interventricular septum defect the pulmonary artery arises. It gives off in an essentially normal manner the right and left pulmonary branches. The position of the ductus arteriosus has been described. The main pulmonary artery is 0.8 cm. in diameter just above its valve and there is no evidence of stenosis.

The lesions in this heart consist, therefore, of complete transposition of aorta and pulmonary artery, with reversal of the usual muscular preponderance of the two ventricles. The right auricle is markedly dilated and hypertrophied. The large patent foramen ovale makes virtually a single chamber of the auricles. The interventricular septum defect is practically closed by granulations so that the minute opening still present is probably of little consequence.

Lungs: Weight of right, 52 gm.; left, 38 gm. The posterior two-thirds of each lung are similar in appearance, being dark red on the pleural surface and boggy. The anterior portions are pink and crepitant. On section, from the anterior portions exudes a pale frothy fluid and from the posterior a bloody, frothy fluid. The alveolar outlines are as a whole quite distinct. The trachea and primary bronchi are normal.

Spleen: Weight, 14 gm. It presents the appearance of chronic passive congestion.

Gastro-Intestinal Tract: Appears normal

Pancreas: Appears normal.

Liver: Weight, 186 gm. It is dark red with a smooth capsular surface. On section much dark red blood escapes from the hepatic veins. The lobules are indistinctly outlined by pale red lines.

Gallbladder, Kidneys, Suprarenals and Bladder: Appear normal.

Aorta: Shows no abnormality in its branching.

CASE 2.—Male, white, aged 3 weeks.

Family History.—Father and mother well. There is no history of miscarriages.

Past History.—He is the second baby and of normal birth. There have been no convulsions nor disturbance of feeding. The baby is brought to the hospital because of marked cyanosis and with the diagnosis of a "bad heart."

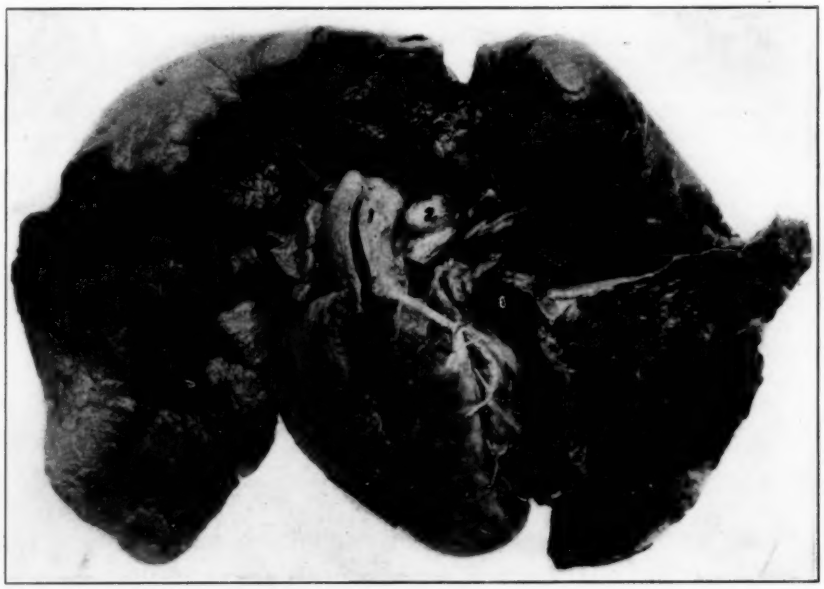

Fig. 2.—Case 2. Heart and lungs, anterior aspect. 1. Aorta. 2. Pulmonary artery. 3. Ductus arteriosus.

Physical Examination.—Baby has marked cyanosis, more especially over the face and becoming worse with crying. There is moderate dyspnea. The lungs are fairly clear throughout. Over the heart a systolic murmur is heard at the base at the junction of the second rib and sternum on the left.

Diagnosis.—Pulmonic stenosis (?). Malformation of the vessels. Roentgen-Ray Report: Slight enlargement of the heart to the left. The right hilus is suggestive of atelectasis. Pulse rate varied between 140 and 150 per minute; respirations from 40 to 60. Death occurred twenty-three days after entrance.

Necropsy Diagnoses.—Complete transposition of aorta and pulmonary artery; patent ductus arteriosus; slightly patent foramen ovale; congestion of thoracic and abdominal viscera: mongolian facies; accessory spleens.

Body is that of a fairly well nourished male, white infant, 50 cm. in length. There are no external stigmata except for slight mongolian aspect of the eyes and some outward bowing of the legs with slightly enlarged epiphyses. The anterior fontanel is open 2 cm. and somewhat depressed.

Peritoneal Cavity: There are no adhesions or free fluid. The organs are in normal positions. The diaphragm on both sides is level with the fourth rib.

Pleural and Pericardial Cavities: Contain no excess of fluid.

Heart: As it lies in situ it appears rather larger than normal in every respect. The left side is soft and collapsed, altering the usual rounded outline of this part of the organ. The ascending aorta is prominent, completely covering from view the pulmonary artery and externally apparently coming off from the right side of the heart. The heart, empty, measures 4.8 by 4.2 cm. There is marked hypertrophy of the myocardium of the right ventricle, the wall being 1.7 cm. in thickness, the left ventricle 0.3 cm. The valves are smooth and glistening and there are no signs of stenosis. The ventricles contain a scant amount of fluid blood. The auricular appendages are empty. There is complete transposition of the great vessels, the aorta coming from the right ventricle immediately to the right of the interventricular septum and the pulmonary artery from the left ventricle, about 0.5 cm. to the left of the septum. The superior and inferior venae cavae enter the right auricle and the pulmonary veins enter the left auricle in a normal manner. There is a patulous ductus arteriosus which measures 1.5 cm. in length with a lumen of 3 mm. extending between the pulmonary artery and the aorta which it joins just beyond the level of the innominate artery. The foramen ovale has a narrow crescentic opening along the lower border, fairly well covered by the limbus. The interventricular septum is entirely closed.

Lungs: Were removed with the heart. They are of a pale, grayish red color, give crepitation and on section the bronchi show some yellowish, frothy fluid escaping. The trachea and bronchi are normal.

Spleen: Weight, 15 gm. It is very dark red and the surface is tense. The pulp is markedly congested. There are two accessory spleens close to the hilum, measuring 2 and 3 mm. in size, respectively.

Gastro-Intestinal Tract: Shows considerable edema and congestion throughout.

Liver: Weighs 98 gm. and is markedly congested.

Kidneys: Weigh 12 gm. each. The fetal lobulations are still conspicuous. The cortex and medulla are moderately congested.

Aorta: There is no abnormality in the size or branching.

DISCUSSION

The developmental errors which result in complete transposition of the aorta and pulmonary artery are chiefly two, according to Rokitansky,[1] who gave the first reasonable explanation for the phenomenon. These are: (a) a deviation of the aortic septum within the truncus aorticus, and (b) its faulty union with the interventricular septum.

Early in fetal life the elongated truncus aorticus is divided into aorta and pulmonary artery by a process in which three factors each play a part. These are, first, a proximal and, second, a distal part of the endocardial swellings in the bulbar part of the truncus aorticus which are known as the proximal and distal bulbar swellings and, third, the aortopulmonary septum. These three elements, at first distinct, later blend to form the spiral septum with its concavity facing posteriorly and to the right, dividing the truncus aorticus into aorta and pulmonary artery. With the ventricles in their normal position any deviation of the septum will cause a change in the relative positions of

1. Rokitansky: Defekte der Scheidewande des Herzens, Vienna, 1875.

the two vessels and transposition will result, the aorta arising from the right ventricle and the pulmonary artery from the left ventricle.

The part played by faulty union of the aortic septum with the interventricular septum may be very important. Quoting from Abbott [2] " . . . in the normal heart, in the union of the aortic and interventricular septa, the latter becomes continuous with the left wall of the aorta in front and with its right wall behind (through the pars membranacea), surrounding the vessel on its right side in such a way that the latter becomes placed in the left ventricle, while the pulmonary artery comes to lie in the right. Should this union take place at an abnormal angle, so that the interventricular septum surrounds the vessels rising posteriorly, on its left instead of its right wall, the trunks will be placed in the reversed cavities and again, even though the trunks may be in a normal relation to each other, transposition will ensue."

Complete transposition is incompatible with long life. Emanuel's patient,[3] who lived eleven years, is the oldest case on record; most patients varied in age from a few days to several months. The maintaining of the pulmonary circulation is of greatest importance, and some means must be provided for supplying oxygenated blood to the aorta. The fetus requires no special mechanism, as the pulmonary circulation has not been established. If in an infant with complete transposition immediately after birth the foramen ovale and ductus arteriosus become closed as normally occurs, then the aorta would be supplied with venous blood from the right ventricle and the pulmonary circulation through the left side of the heart and lungs would be a closed circuit. However, cardiac anomalies are seldom single, particularly in the major errors and some means which, nevertheless, is almost always insufficient is provided for passage of oxygenated blood from the pulmonary system to the aorta.

The usual accessories are a patent foramen ovale, a patent ductus arteriosus, a perforate interventricular septum or combination of these. With a widely open foramen ovale blood from the lungs can pass back into the right auricle to escape into the aorta through the right ventricle. Case 1 had such a channel and lived a year even with a patent interventricular septum closed by granulations. An open ductus arteriosus is probably seldom of sufficient caliber to compensate as well as a fully open foramen ovale and Case 2 with a very slight aperture for a foramen and a patent ductus with a caliber of about 3 mm. was insufficient to supply oxygenated blood to the systemic arterial circulation, the patient living but six weeks.

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2. Abbott: Osler's Modern Medicine **4**:368.
3. Emanuel: Reference in Abbott's Article, Osler's Modern Medicine **4**:368.

In Case 1 there was also an acquired tricuspid insufficiency. With this additional lesion the mechanics of the circulation might be explained as follows: During right auricular systole, blood would be propelled both through the tricuspid valve and through the foramen ovale. However, at systole of the left auricle there would tend to be a current through the foramen from left to right. This blood would be oxygenated and be mixed with the venous blood of the right auricle but likely not in equal proportions on account of the muscular preponderance of the right side of the heart and the regurgitation through the tricuspid valve. These two factors would produce a pressure in the right auricle greater than that in the left and a mixture of blood from the two sides made difficult. Consequently, there would tend to be an anoxemia in the systemic circulation and it is thus seen that the tricuspid insufficiency undoubtedly was an important contributory factor in the death of the patient.

In Case 2 there was a foramen ovale of very small proportions, too small to give any symptoms in an otherwise normal heart. The ductus arteriosus was open but its lumen was too small to compensate for the abnormal origin of the great vessels. The life of the child was consequently of short duration, six weeks, in striking contrast to the first child with a widely patent foramen ovale and who lived a year.

THE RESISTANCE TO ACUTE DISEASE OF THE RESPIRATORY TRACT IN CHILDREN *

JOHN ZAHORSKY, M.D.

ST. LOUIS

In another article [1] I referred to the relative immunity which develops in children from the seventh to the ninth year. While this conception is common among physicians, I do not know of any study which shows this in plain figures.

I have gone over my records for six years (1913-1918) and tabulated the age of the children who were seen suffering from acute disorder of the respiratory tract. This series embraced the following diseases: Coryza, adenoiditis, otitis media, pharyngitis, tonsillitis, laryngitis, tracheitis, bronchitis, bronchiolitis, bronchopneumonia and pneumonia; cases of grippe, colds and coughs were also included. Cases of Spanish influenza occurring during the epidemic of 1918-1919, were excluded.

It should be remembered, however, that this does not include all the cases occurring in families. Many mild cases and so many "colds" in older children do not produce sufficient anxiety to the parent so that a physician's advice is sought. The curve, then, represents the age incidence of respiratory diseases, the symptoms of which were sufficiently intense to cause the parent apprehension. The milder reactions of the respiratory tract are generally called "colds" and are treated by home remedies.

DATA AS TO AGE, BASED ON 2,896 CASES

Age	Cases
From 0 to 1 year	503
From 1 to 2 years	393
From 2 to 3 years	318
From 3 to 4 years	285
From 4 to 5 years	302
From 5 to 6 years	357
From 6 to 7 years	277
From 7 to 8 years	172
From 8 to 9 years	93
From 9 to 10 years	65
From 10 to 11 years	47
From 11 to 12 years	35
From 12 to 13 years	29
From 13 to 14 years	20

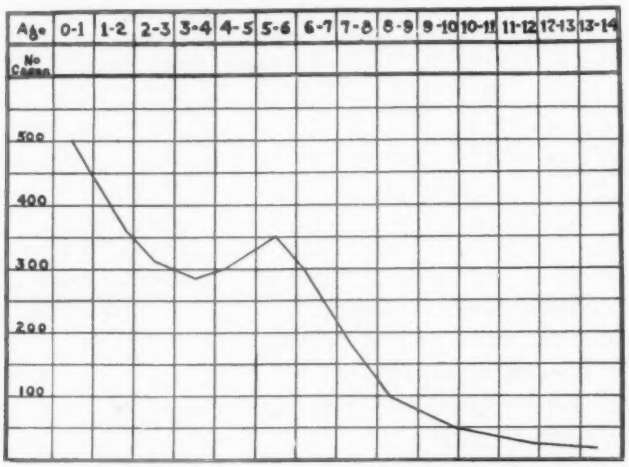
* Received for publication Sept. 10, 1920.

1. Zahorsky, J.: Interstate M. J. **26**:67, 1919.

These figures are plotted in a curve. A study of this curve shows, first, the precipitous decline of the incidence of acute respiratory diseases after the seventh year. It corroborates the popular belief that the body changes at the seventh year. While "colds" still occur, they are less severe and less frequent.

The extremely high incidence in infancy, which this curve shows, must be modified by the well known fact that parents are prone to send for a physician for trifling ailments in infants; also that infants react more severely to respiratory infections. It is extremely doubtful whether disease of the respiratory system is more frequent at 1 year than at 3 years.

A curious phenomenon is found in the sudden elevation at the fifth and sixth year. This corresponds to the beginning of school life.



An analysis of a large number of these cases at this age demonstrates that two factors are operative: (1) the extreme susceptibility of many children who have not been exposed to a variety of respiratory infections until they enter school; (2) the frequent repetition of respiratory disease in some children at this age (recurrent tonsillitis, recurrent bronchitis).

It is clear from this study that most persons develop a relative immunity to respiratory infections in early childhood. This immunity is acquired gradually but is subject to many fluctuations in severity during the process of development. Several mild attacks may be followed by a severe attack; or one or more local diseases with no general reaction may precede a serious disease with marked constitutional symptoms. Nevertheless, taking a large number of children, this gradual increase in the resistance may be plainly discerned.

I distinguish three stages in the development of this resistance: (1) infantile resistance, (2) puerile resistance and (3) normal resistance.

The infantile resistance to respiratory infections, as its name implies, is found mostly in infants. It is characterized by several features. The infant is less able to resist the morbific agents and the disease spreads throughout the respiratory tract. The coryza nearly always terminates in a bronchitis or bronchopneumonia. Hence, an extensive invasion of the respiratory tract is the most marked peculiarity of infantile resistance.

Another distinctive character is the presence of general symptoms. Fever, prostration, restlessness, anorexia and loss of weight are generally present in infants even when the pathogenic agent is slightly virulent, as in the common cold. Then, there is the development of adenopathy, which becomes most marked when the infectious agent is very virulent. Then suppuration is frequent. The great tendency to otitis media and bronchopneumonia is characteristic of the infantile resistance. The duration of the disease also is longer than in the older child.

Puerile resistance is characterized by an invasion of only a part of the respiratory tract and a fleeting appearance of general symptoms. The disease tends to remain localized but the febrile reaction may still be great; the duration, however, is short. Adenopathy, except tonsillitis, is uncommon and otitis media and bronchopneumonia become less frequent.

A normal resistance is shown when there is only a localized reaction and no febrile disturbance. A coryza, a pharyngitis, laryngitis, or tracheitis may develop, but except for a few days' lassitude and the annoyance of the local symptoms, the patient is not sick.

These different stages of resistance are not limited to the ages indicated by the curve of incidence. Thus, a child may persistently show an infantile resistance throughout the whole period of childhood. These children are well known to pediatrists. Every time the grippe occurs in a family, the susceptible child shows a serious bronchitis or bronchopneumonia. On the other hand, the baby may be born with a normal resistance, that is, he never acquires anything more severe than a common "cold." Then, again, the child may show a normal resistance until he enters school and for many months an infantile or puerile resistance is manifested. An acute infectious disease, such as whooping cough, measles, etc., may alter the resistance for months. A chronic infected focus—tonsil, tooth or gland—often changes the type of resistance.

The value of having some clinical standards whereby we gage the resistance of an infectious disease is unquestionable. Whether the suggestion that we distinguish three grades of resistance is really useful remains to be seen. However, there is a great difference in children in their resistance to the respiratory infections, and since we must depend in the prophylaxis and cure of these common diseases almost entirely on this resistance, every little effort to elucidate the subject will be serviceable.

THE DIAGNOSIS AND PROGNOSIS OF TUBERCULOSIS IN INFANCY*

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In 1914, under the stimulus of the ability to examine postmortem material in a large percentage of fatal cases at the Infants' Hospital, we began a detailed study of tuberculosis in the first two years of life. This study while, perhaps, not disclosing anything very startlingly new, has given results which may be of value in emphasizing certain peculiarities of the disease at this period of life, and which have the advantage of being based on a series of necropsies on children under 2 years of age which is larger than any we have been able to find in the literature, at least in American literature. The conclusions presented in this paper are based on a series of 374 cases in which a clinical diagnosis of tuberculosis was made in the wards of the Infants' Hospital, and on a series of 138 necropsies in which lesions of tuberculosis were found.

DIAGNOSIS OF TUBERCULOSIS

The material obtained in this study will first be considered in connection with the question of the diagnosis of tuberculosis in the first two years of life. The frequency with which there was found postmortem a tuberculous infection not suspected during life suggested the imperfection of a diagnostic method confined to mere routine examination of the lungs for evidences of consolidation. The incidence of tuberculosis at necropsy is placed by Hamburger at 23 per cent. in babies 1 year old, and at 40 per cent. in babies 2 years old. These figures probably have wide variations according to locality. In our series of 661 consecutive necropsies in children under 2 years, 138, or 20 per cent., showed tuberculous lesions. This frequency suggests how often the presence of the disease is overlooked clinically.

Hamburger divides tuberculosis into three stages, primary, secondary, and tertiary—the primary stage being represented by the primary lesion and the associated lymph node involvement; the secondary stage being represented by all the lesions produced by the further invasion of the body by the tubercle bacillus, and the tertiary stage being represented by the chronic destructive lesions, such as the bone and joint tuberculosis of later childhood, and the phthisis

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of adult life. We believe that this division into stages is not only advantageous but actually essential in the study of infantile tuberculosis. Every case in the entire series, both clinically and at necropsy, fell clearly and definitely into either the primary or the secondary stage as described by Hamburger.

In looking back over a series of records made before the beginning of the investigation which is the basis of this paper, we were impressed by the fact that the clinical diagnosis of tuberculosis in infancy was based on one of two classes of evidence. The first was the existence of some form of easily recognized clinical tuberculosis, such as tuberculous meningitis, tuberculous peritonitis, or tuberculous pleurisy. The second was the finding in the lung of evidences of chronic consolidation, with such confirmatory evidence as an up and down temperature curve, wasting and, perhaps, a positive von Pirquet reaction. The first class of cases are obviously of the secondary stage of the disease. In the second class of cases, those with evidence of pulmonary consolidation, the postmortem findings were almost invariably described as tuberculous bronchopneumonia. Therefore, it appears that the diagnosis of tuberculosis, when based on the two classes of evidence mentioned, is really *based on the existence of the secondary stage of the disease*, because tuberculous meningitis, peritonitis, pleurisy and bronchopneumonia are all secondary lesions. This means that in the series of records made before the beginning of the detailed investigation, the diagnosis was only made when the secondary stage had been reached. Meanwhile, necropsies made during the same period every now and then disclosed cases in which no clinical diagnosis of tuberculosis had been made, but in which at the postmortem examination only the lesions of the primary stage were found. It thus appeared that the diagnosis of tuberculosis in infancy in the primary stage was extremely difficult to make under ordinary routine methods of examination.

A study of our necropsy records taken from the period previous to the beginning of this detailed investigation also disclosed another difficulty. It appeared that the existence of chronic signs of pulmonary consolidation, even when associated with an up and down temperature curve and loss of weight, did not warrant a positive diagnosis of tuberculous bronchopneumonia. In many of these cases there was a chronic or unresolved bronchopneumonia, due to another cause, and showing no tuberculous tissue changes. It appeared, therefore, that even when signs of pulmonary consolidation are present, the diagnosis of tuberculosis must depend on more than the ordinary methods of examination. It is only when such definitely recognizable secondary lesions as meningitis or peritonitis are present, that the diagnosis can be made easily.

METHOD OF EXAMINATION

As a result of these observations, the following methods were adopted as a routine in the examination of the babies admitted to the hospital: The lungs were examined not only for signs of consolidation, but also for signs of enlargement of the tracheobronchial lymph nodes. The signs specially looked for were interscapular dulness, prolongation downward of the normal cervical dulness, and d'Espine's sign. The von Pirquet cutaneous reaction was tested, and repeated at intervals. In all cases which showed signs of pulmonary consolidation, or of bronchial lymph node enlargement, or which gave a positive von Pirquet reaction, or in which there was any other reason to suspect tuberculosis, such as exposure or unexplained loss of weight, a roentgenogram of the chest was taken. It proved impossible to carry out this method of investigation as thoroughly as we could wish. With whatever evidence was obtained as a basis, a decision was made as to the presence or absence of tuberculosis. After committing ourselves, the postmortem findings were carefully studied in every case in which a necropsy was performed, and whenever possible the subsequent history of the patients discharged from the hospital with the diagnosis of tuberculosis was followed. We learned a great deal from this procedure, owing to the number of necropsies which were available. It is what we learned that we shall endeavor to present.

TABLE 1.—ANALYSIS OF 374 CASES

	Cases
Diagnosis of tuberculosis made	374
Total admissions to hospital in same period	3,100
Diagnosis confirmed	291
Diagnosis confirmed by necropsy	129
Total necropsies in same period	661
Diagnosis confirmed by subsequent clinical developments	153
Diagnosis remained unconfirmed	78
Diagnosis contradicted by necropsy findings	5
Diagnosis not made clinically in cases found tuberculous at necropsy	9

Table 1 is an analysis of the series with reference to the correctness of the diagnosis made under the methods employed.

The series shows, as a first point of interest, the frequency of clinical tuberculosis in hospital patients under 2 years of age. In 12 per cent. of all our admissions a clinical diagnosis of tuberculosis was made, and in 9 per cent. of all admissions this diagnosis was confirmed. The relative frequency of tuberculosis at necropsy, 20 per cent., is, of course, higher than the clinical frequency, on account of the tendency of the disease to end fatally in the first two years of life.

CONFIRMATION OF DIAGNOSIS

The diagnosis of tuberculosis was considered as confirmed in two ways. One was the finding of tuberculous lesions at necropsy; the

other was the presence or subsequent development of unmistakable clinical types of the disease. The types regarded as unmistakable were typical cases of tuberculous meningitis, peritonitis, pleurisy, or cervical adenitis, or cases showing such clearly tuberculous lesions as Pott's disease or dactylitis, or the clinical finding of tubercle bacilli. No case in which a diagnosis of tuberculous bronchopneumonia or chronic pulmonary tuberculosis was made was placed in this unmistakable group. This confirmation was obtained in some cases by the presence or development of an unmistakable type while the patient was still in the hospital; in other cases it was obtained by the development of such a secondary type in the cases followed through our Social Service Department. Cases in which tubercle bacilli were found in the sputum or in discharging ears were included in this group. There were twenty cases in which tuberculids were found on the skin. The cases in which the diagnosis was confirmed by postmortem examination form the larger group and their number was the most encouraging feature in leading us to continue this method of clinical study.

TABLE 2.—Analysis of the Diagnostic Value of Special Methods of Examination with Reference to Clinical Findings

A. Unmistakable Forms	Cases	Confirmation			Von Pirquet			D'Espine			Roentgen Ray		
		Necropsy	Clinical Development	Unconfirmed	+	0	?	+	0	?	+	0	?
Tuberculous meningitis	124	77	47	0	46	26	1	40	21	13	38	2	8
Tuberculous peritonitis	19	4	11	4	9	7	2	1	13	1	1	5	3
Tuberculous pleurisy	1	0	1	0	1	0	0	1	0	0	1	0	0
Tuberculous cervical adenitis	1	0	1	0	1	0	0	0	0	1	1	0	0
Bone and joint tuberculosis	1	0	1	0	1	0	0	1	0	0	0	0	1
Total	146	81	61	4	58	33	3	43	34	15	41	7	12
B. Forms Presenting Difficulty in Diagnosis:													
Chronic primary tuberculosis	135												
a. Pulmonary	126	2	58	66	76	37	7	71	12	53	68	8	18
b. Intestinal	9	2	2	5	3	2	0	0	9	0	1	8	0
Tuberculous bronchopneumonia	34	10	21	3	16	15	1	20	9	14	20	0	8
Miliary tuberculosis (without meningitis)	54	43	11	0	25	23	0	24	17	11	28	1	5
Total	223	57	92	74	120	77	8	115	47	78	117	17	31
Grand total	369	138	153	78	178	110	11	158	81	93	158	24	43

Table 2 shows the series of cases analyzed with reference to the clinical diagnosis, and the presence or absence of the evidence through which the forms presenting difficulty in diagnosis are to be recognized.

It will be noted that in many cases the von Pirquet test, the examination of the chest for interscapular dulness and d'Espine's sign or

the roentgenogram were negative. Nevertheless, in the second group, showing the presence or absence of these signs in forms of tuberculosis presenting difficulty of diagnosis, *a diagnosis of tuberculosis was not made in any case unless at least one of these three signs was positive.*

Table 3 shows the presence or absence of the same three signs, taken not with reference to the clinical diagnosis, but with reference to the confirmation of the diagnosis by necropsy or otherwise. Of course, in all the cases of tuberculous meningitis in the series the diagnosis was also confirmed by lumbar puncture.

TABLE 3.—THE DIAGNOSTIC VALUE OF SPECIAL METHODS OF EXAMINATION WITH REFERENCE TO NECROPSY FINDINGS

	Cases	Von Pirquet			D'Espine			Roentgen Ray		
		+	0	?	+	0	?	+	0	?
A. Confirmation by necropsy	143	59	37	2	80	32	31	48	11	18
1. Primary lesions only	4	3	1	0	2	2	0			
a. Lung	2	1	1	0	2	0	0	1	0	1
b. Intestine	2	2	0	0	0	2	0	0	2	0
2. Secondary lesions found	125	53	30	0	74	22	29	44	9	15
3. Clinical diagnosis not made; necropsy showed primary lesions of tuberculosis	9	0	5	0	0	7	2	None made		
3. Clinical diagnosis of tuberculosis; necropsy failed to confirm	5	3	1	0	4	1	0	3	0	2
B. Confirmation by clinical developments	153	61	51	5	44	32	27	85	8	17
C. Clinical diagnosis unconfirmed	78	61	23	6	38	18	35	28	5	10
Total	374	181	111	11	162	82	93	161	24	45

DIAGNOSTIC VALUE OF TUBERCULIN TEST

The von Pirquet reaction was present in the majority of cases. Comparison of our results with necropsy findings would suggest that the reactions designated as "suspicious" or "doubtful," should in the infant be considered as positive for purposes of diagnosis. Nevertheless, the reaction was negative in a fairly large proportion of cases in which the diagnosis of tuberculosis was confirmed either by necropsy, or by the development of some unmistakable type of secondary lesion. We believe that the comparatively high proportion of negative von Pirquet reactions obtained in tuberculous infants under 2 years is to be explained by the frequency of marked atrophy and anemia, which prevents the showing of a positive test. We must assume from our results that the presence of a negative von Pirquet in no way rules out the diagnosis of tuberculosis in an infant under 2 years of age.

The diagnostic value of a positive von Pirquet reaction in the infant appears to be much greater. In only five cases in our series

did the necropsy findings fail to confirm the clinical diagnosis of tuberculosis. In only three of these cases was the von Pirquet reaction recorded as positive. It is, therefore, safe to conclude that in an infant under 2 years of age, a diagnosis of tuberculosis with very little chance of error may be made when a positive von Pirquet reaction is obtained.

DIAGNOSTIC VALUE OF PHYSICAL SIGNS

The examination of the chest for interscapular dulness and d'Espine's sign is important. When no spinal dulness or bronchial breathing is obtained below the level of the second dorsal vertebra, the sign should be considered negative. When the level is the third dorsal vertebra, the sign should be considered as doubtful, and no conclusion can be based on these signs alone. When the spinal dulness and bronchial breathing are found below the level of the third dorsal vertebra, the sign should be considered as positive in cases without signs of pulmonary consolidation, and a diagnosis of tracheobronchial lymph node enlargement, presumably tuberculous, may be made. When there are signs of consolidation of the lung, they often mask d'Espine's sign and interscapular dulness, and caution must be exercised. Tuberculosis should not be diagnosed without other evidence in these cases. In our series, this method of examination was positive in 48 per cent., doubtful in 27 per cent. and negative in 25 per cent. It was negative in 22 per cent. of the cases which came to necropsy. In the primary stage of the disease, our necropsy statistics suggest that a diagnosis of tuberculosis based on a positive d'Espine's sign or interscapular dulness, or both, will be right in the majority of cases. A negative finding does not rule out tuberculosis, and is of course always the rule in cases of primary intestinal tuberculosis.

DIAGNOSTIC VALUE OF ROENTGENOGRAMS

The examination of roentgenograms of the chest eventually proved to be the diagnostic method on which we placed the greatest reliance. Practice in interpreting plates is necessary, and this can only be gained by the comparison of clinical conclusions with necropsy findings. It is necessary to know what tuberculous lesions of the chest are shown and what are not shown in roentgenograms. Four lesions in the chest are characteristic of the tuberculosis of infancy. These are, first, primary lesions in the lung; second, the accompanying enlargement and caseation of the tracheobronchial lymph nodes; third, miliary tuberculosis of the lung, and fourth, tuberculous bronchopneumonia.

The primary lesion of the lung is usually not shown in the rentgenograms; it is too small. There were only one or two cases in our series in which there was found at necropsy a primary lesion large

enough to give a shadow on a photographic plate. The enlargement and caseation of the bronchial lymph nodes can be seen in the majority of roentgenograms. This appears as a definite and characteristic shadow at the hilus of the lung, but much practice is required in distinguishing this shadow from certain shadows found at the hilus in normal infants. Congenital pulmonary atelectasis and thymic enlargement occasionally lead to a mistaken diagnosis. Acute miliary tuberculosis of the lung does not show in roentgenograms in the majority of instances. This is proved by a large series of negative roentgenograms obtained in cases showing this lesion at the necropsy. In the earlier cases of our series we frequently made a diagnosis of acute miliary tuberculosis of the lungs when the plates showed a peculiar spotted appearance. In the majority of cases of this kind which came to necropsy, the postmortem finding was tuberculous bronchopneumonia. Nevertheless, there were in the series a few spotted plates which showed no bronchopneumonia but showed a miliary tuberculosis of the lung with the formation of large conglomerate tubercles. Finally, tuberculous bronchopneumonia invariably shows in roentgenograms a shadow recognizable as pulmonary consolidation, but not always recognizable as tuberculous. We shall have more to say about these plates in considering the diagnosis of this form of infantile tuberculosis.

Roentgenograms of the chest were positive in 70 per cent. of the observations made in our series; positive or suspicious in 89 per cent.; negative in 11 per cent. These figures show their great diagnostic value in tuberculosis of the first two years of life. Necropsy findings also suggested that most of the roentgenograms recorded as doubtful or suspicious should have been considered positive. Negative roentgenograms in cases which came to necropsy were recorded in only 14 per cent. We may, therefore, conclude that a diagnosis of tuberculosis may be made by any one practiced in interpreting roentgenograms whenever the roentgenogram is positive for tracheobronchial lymph node enlargement. A negative plate, however, does not rule out tuberculosis.

DIAGNOSIS OF THE PRIMARY STAGE

In general, as far as the diagnosis of the primary stage of tuberculosis is concerned, the following conclusions appear to be warranted: A positive von Pirquet reaction is the only evidence pointing toward a primary intestinal infection, and the diagnosis of this form of the disease cannot be made unless either the von Pirquet is positive or the physician is fortunate enough to find tubercle bacilli in the stools. Primary intestinal tuberculosis is, however, very rare in comparison with a primary focus in the lung, and it is in the recognition of this

latter condition that special methods of diagnosis are particularly needed. If either the von Pirquet reaction is positive or even suspicious, or if the roentgenogram of the chest shows the shadow characteristic of tracheobronchial lymph node enlargement, a diagnosis of tuberculosis primary in the lung may be made with a fair degree of certainty. If the sole evidence is a positive or even suspicious d'Espine's sign, or interscapular dulness, the diagnosis may be made with only a slight degree of probability.

TABLE 4.—DIAGNOSTIC SIGNS IN CASES SHOWING PHYSICAL SIGNS OF PULMONARY CONSOLIDATION

Necropsy Findings	Cases	Von Pirquet			D'Espine			Roentgen Ray		
		+	0	?	+	0	?	+	0	?
Tuberculous broncho-pneumonia	42	21	10	1	38	1	3	20	1	5
Chronic primary tuberculosis plus nontuberculous pneumonia	4	3	0	0	2	1	1	1	0	3
Nontuberculous pneumonia without primary tuberculous lesions	5	3	1	0	4	1	0	3	0	2

In all cases in which all three of these forms of evidence are absent, tuberculosis in the primary stage should not be diagnosed. In cases of the secondary stage of the disease the diagnosis so frequently depends on ordinary clinical evidence that these special methods of investigation are unnecessary. There are, however, two secondary forms of the disease in which the diagnosis is more difficult. These are tuberculous bronchopneumonia and general miliary tuberculosis involving the lung and abdominal organs but in which the brain is spared.

POSITIVE DIAGNOSTIC VALUE OF PULMONARY CONSOLIDATION

The characteristic sign of tuberculous bronchopneumonia in the infant is the finding of evidence of pulmonary consolidation. In general, these cases tend toward a rather chronic course, but some of them are fully as acute as ordinary cases of nontuberculous pneumonia. No very reliable conclusion can be drawn from the extent and distribution of the consolidation as shown by physical examination. It is important in all these cases to determine whether the consolidation is due to a tuberculous pneumonia or to a pneumonia from some other cause. For this purpose we must rely on the same general signs of tuberculosis as we have considered in connection with the primary stage of the disease, namely, the von Pirquet reaction, the examination of the chest for signs of tracheobronchial lymph node enlargement, and the results of roentgenograms of the chest.

Table 4 shows these diagnostic signs in the cases of our series in which a diagnosis of tuberculous bronchopneumonia was made and confirmed at necropsy findings.

We may conclude from these statistics that in the majority of cases showing pulmonary consolidation, in which either the von Pirquet reaction or the roentgen ray is positive, the correct diagnosis is tuberculous bronchopneumonia. In a few cases, however, the diagnosis of tuberculosis will either be wrong, or else there will be a combination of the primary stage of tuberculosis with a nontuberculous pneumonia. Roentgenograms will usually permit the observer to distinguish between tuberculous and nontuberculous pneumonia. In the tuberculous form the shadows are much more distinct and sharply outlined. Many plates show the characteristic speckled or spotted appearance which is never seen in nontuberculous pneumonia. When there are large areas of consolidation the shadows are usually much more dense than in nontuberculous pneumonia. It should be remembered, however, that occasionally a speckled or spotted plate means acute miliary tuberculosis of the lung with conglomerate tubercle formation and without the lesion of pneumonia. Such cases may, however, be recognized through the absence of signs of consolidation of the lung on auscultation and percussion.

PROGNOSIS

The analysis of the outcome of the disease to date in the cases in our series as shown by the hospital mortality and the subsequent mortality or present condition of the cases discharged from the hospital, is interesting as bearing on the prognosis of tuberculous infection when acquired during the first two years of life. This is shown in Table 5.

TABLE 5.—Outcome in 369 Cases Diagnosed as Tuberculosis

	Cases
Died in hospital	194
Discharged living	175
Present condition unknown	50
Present condition known	125
Died after discharge	82
Alive and well	43

The mortality in the hospital was as high as 53 per cent. This, of course, does not give any accurate idea of the fatality of tuberculous infection in the first two years of life, because infants who seek hospital treatment are apt to show the more serious forms of the disease. It does suggest, however, the great prevalence of acute and fatal forms of the disease in the first two years of life.

Of the patients who died in the hospital, the cause of death in 188 was the existence or development of some severe form of the

secondary stage of the disease. Of these secondary forms, tuberculous meningitis was the most common, tuberculous bronchopneumonia standing next in frequency. (Miliary tuberculosis without meningitis was a rare clinical diagnosis, but was the most common lesion found at necropsy, being present in almost every case of tuberculous meningitis, in many cases of tuberculous pneumonia, and occasionally being the only secondary lesion.) In the remaining six cases, only the lesions of the primary stage were found, and to these may be added the nine cases in which the diagnosis was not made during life, which also showed only lesions of the primary stage. In these fifteen cases, the tuberculosis could only be considered a contributing cause of death, as all the patients were admitted to the hospital for functional cases of that character.

TABLE 6.—DIAGNOSIS AT DISCHARGE AND FINAL OUTCOME IN 175 CASES

	Cases	Living	Died	Lost
Primary stage	123	38	43	42
Tuberculous meningitis	14	0	14	0
Tuberculous bronchopneumonia	14	1	11	2
Tuberculous peritonitis	14	0	8	6
General miliary tuberculosis	7	1	6	0
Tuberculous cervical adenitis	1	1	0	0
Tuberculous pleurisy	1	1	0	0
Bone and joint tuberculosis	1	1	0	0
Total	175	43	82	50

Of the patients discharged from the hospital, the diagnosis at the time of discharge with the present condition of the patient is shown by Table 6.

This table shows that the majority of the patients now living showed at the time of their discharge from the hospital only the primary stage of the disease. The patients in this stage who were followed to a subsequent fatal ending all developed a serious secondary form which was the cause of death. It is also an interesting fact that *this secondary form usually developed within a comparatively short time after discharge, usually within the period of infancy, that is, before the end of the second year of life.*

We may conclude from the subsequent history of these cases, that *the prognosis of infantile tuberculosis is best when the patient shows evidence that the disease has not advanced beyond the primary stage, but is still not good,* owing to the tendency of the infant to develop fatal forms of the secondary stage. This tendency is greatest in infancy, grows less as the child grows older.

The figures from the forms of the secondary stage show that only tuberculous meningitis or general miliary tuberculosis are absolutely fatal. In all the other forms of tuberculosis there is a possibility of

recovery, but the prognosis is much worse than in the primary stage. In the first place, these types may be fatal in themselves, tuberculous bronchopneumonia being the most serious next to the miliary forms. Not only, however, is there this danger, but also in all these forms there is the same tendency toward the development of meningitis or miliary tuberculosis as was seen in the primary stages, this tendency being greatest in infancy.

If it were not for this tendency, characteristic of infancy, toward the development of severe secondary forms of tuberculosis, we would have little evidence of the value of our diagnostic methods in recognizing the disease while the patient was still in the primary stage. Comparatively few persons whose condition was diagnosed as being in this stage of the diease came to necropsy; the majority left the hospital alive. But their subsequent histories and mortality substantiated the diagnosis so frequently, that we believe that the recognition of the primary stage of the disease can be made in most cases through the use of the von Pirquet reaction, roentgenograms, and careful examination for the physical signs of tracheobronchial lymph node enlargement. The importance of making the diagnosis in this stage is evident from the peculiarities of the prognosis of tuberculous infection acquired in infancy. This prognosis is bad. Would it be so bad if the presence of tuberculosis in the infant were recognized earlier, and proper treatment instituted as early as possible? This could only be done by means of a systematic and thorough examination of every infant with special reference to tuberculosis. We believe that the physician should consider the possibility of tuberculous infection in the case of every infant that comes under his care. That the infant shows no evidence of being sick should make no difference, for if the disease is in the primary stage, no symptoms suggesting tuberculosis are manifested, but the child will either seem well, or else present itself as a "feeding case," showing only symptoms of functional gastrointestinal disturbance.

We have heard the very harmful and meaningless word "pretuberculous" applied to infants. We have heard the term "latent" or "inactive" tuberculosis applied to infants with the implication that there was little or no danger. Physicians should recognize that an infant is either tuberculous or it is not. If there is one tubercle bacillus, or the smallest tuberculous lesion within the body, the infant is tuberculous. There is no "healed tuberculosis" in the infant. If the tuberculous lesion is latent, inactive, it is better than if the infant had tuberculous meningitis, but the infant is none the less in danger. It is not difficult to make the von Pirquet test on every infant seen, nor to examine the back for interscapular dulness and d'Espine's sign.

Often the diagnosis can be made without a roentgenogram, but one should be made in as many cases as possible.

We believe that if this procedure were more generally carried out, many more cases of infantile tuberculosis would be recognized while in the primary stage. There is so little provision near Boston for the proper treatment of tuberculous infants, that we cannot quote results, but we believe that with earlier recognition of tuberculosis in the infant and with the institution of appropriate treatment, there would be fewer cases seen of dangerous or fatal secondary stage forms, fewer deaths, fewer despairing mothers receiving the verdict which goes with tuberculous meningitis, and asking how such a thing could have occurred in a baby who has always seemed so well.

A NEW APPARATUS AND METHOD FOR PUNCTURING THE SUPERIOR LONGITUDINAL SINUS IN INFANTS*

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NEW YORK

The use of the superior longitudinal sinus to obtain blood for examination and as a path for intravenous injections is attended with many advantages. These advantages are readily appreciated and are emphasized in a number of recent papers. The first to use this vessel was Marfan,[1] in 1898, for the introduction of salt solution in a case of cholera infantum. Nothing further appeared in the literature regarding its use until 1915, when Tobler[2] studied the anatomic relations of the sinus for this purpose. While sinus therapy is now generally regarded a safe procedure, the fact, however, that the sinus is hidden from view, and that there is danger of infiltration into the brain when injecting fluid, justifies a consideration of technic.

Goldbloom,[3] in 1918, devised an apparatus which was an improvement upon several which preceded it. In March, 1920, he[4] described a new apparatus in which the block was beveled at an angle of 50 degrees. The great disadvantage of Goldbloom's apparatus is that the block is so large (and the beveled block gives even a larger surface) that it entirely obliterates the point of the needle from view. It is obvious, therefore, that to insert the needle into the exact spot decided on is somewhat a matter of chance. The fact that in the improved apparatus the needle enters at an angle of 50 degrees does not eliminate the possibility of injury to the sinus wall, as the angle is not sufficiently acute to make the needle run parallel with the sinus after it has been entered. If the needle has been set too long and put in obliquely, it may transfix or penetrate the wall of the sinus. Other disadvantages are that the apparatus is very expensive and a special needle is required should it become too dull for use.

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* Received for publication, Sept. 2, 1920.

* From the Pediatric Service of the New York Nursery and Child's Hospital and the Department of Pediatrics, Cornell University Medical College.

1. Marfan (from Blechmann, G.): Technique des prélévéments de sang et des injections intraveineuses chez les nourrissons, Le Nourrisson **2**:150, 1914.

2. Tobler, L.: Zur technic der diagnostischen blutentnahme und der intravenösen injection beim saügling, Monatschr. f. Kinderh. **13**:384, 1915.

3. Goldbloom, A.: A New Apparatus for Puncture of the Superior Longitudinal Sinus, Am. J. Dis. Child. **16**:388 (Nov.) 1918.

4. Goldbloom, A.: An Improved Needle for Sinus Therapy, Am. J. Dis. Child. **19**:229 (March) 1920.

Owing to disadvantages of the various methods in use, I have devised an apparatus which is simple, inexpensive and presents, I believe, many advantages. It has been used on a large number of infants in the New York Nursery and Child's Hospital and has proved satisfactory.

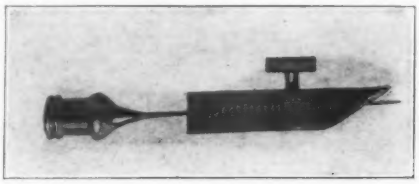

Fig. 1.—Author's Apparatus.

It consists of a small metal block, ¼ of an inch square by 1¼ inches long, with an acutely beveled base. An opening of 18 gage bore runs through the middle of the block which permits the insertion of the needle. A thumb screw is provided which holds the needle securely in place after it has been adjusted to the desired length. The needle is 1⅜ inches long with a Luer-slip hub and a short beveled point.

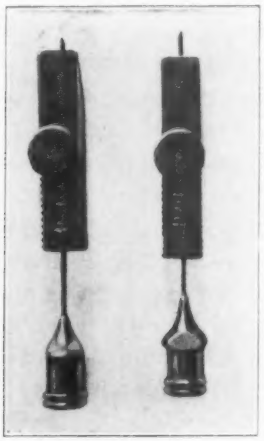

Figure 2

Figure 3

Fig. 2.—Position to adjust length of needle.
Fig. 3.—First step for injecting fluid.

The first step in using the apparatus is to determine the length of the needle necessary to just enter the sinus. There is no exact way of doing this as the depth of the sinus varies somewhat in different infants. A method which I have found helpful is to pinch up a portion of the scalp and half the thickness of the fold gives the approximate depth into the sinus. With the needle as in Figure 2, it is adjusted to the length decided on and the set screw is tightened, keeping

the bevel of the needle in the same direction as the bevel of the block. Tobler's measurements show that the distance from the skin to the sinus is from 2 to 5 mm. and the depth—at the posterior angle—varies between 4 and 7 mm., depending on the age and size of the infant. This would give a range of from 3 to 6 mm. to just enter the sinus in the various cases. Keeping these figures in mind serves as a control.

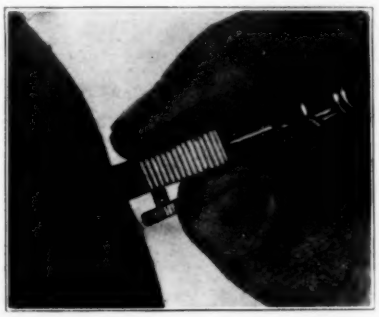

Fig. 4.—Second step for injecting fluid.

Figure 5

Figure 6

Fig. 5.—Third step for injecting fluid.
Fig. 6.—First step for collecting blood.

The point of entrance is chosen near the posterior angle of the fontanel along an imaginary line drawn between the middle of the bridge of the nose and the posterior angle of the fontanel. For the administration of fluid the apparatus, held as in Figure 3, is forced in—at the point decided on—up to the end of the block (Fig. 4). If one has successfully entered the sinus, there will be an immediate and steady flow of blood, and now using the end of the block as a fulcrum, the apparatus is quickly turned so as to bring the beveled

surface of the block in close apposition to the scalp (Fig. 5). A syringe or gravity apparatus is immediately attached to the hub, and the fluid is administered in the usual manner. When the operation is completed, the needle is pulled out, a compress is held firmly over the bleeding point, and the child is raised to a sitting position. After the bleeding has stopped, collodion is applied. For the collection of blood the apparatus is used as shown in Figures 6, 7 and 8.

If one has not entered the sinus successfully, the needle may have been set too short or too long. It may have become blocked, or it may have been inserted outside the sinus. Under such conditions it is time saving immediately to withdraw the needle, determine where the fault lies and correct it. Whenever the needle has been used, it should immediately be cleansed with running cold water;

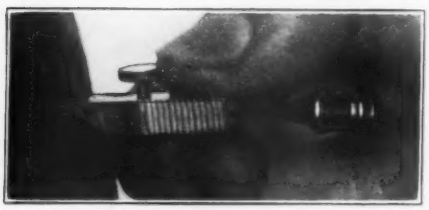

Figure 7

Figure 8

Fig. 7.—Second step for collecting blood.
Fig. 8.—Third step for collecting blood.

the wire run through with a cleaning powder or sapolio until the lumen is clean, rinsed in cold water, then alcohol, and finally immersed in ether. This will keep the apparatus in perfect condition and obviate another cause of faulty venipuncture.

The advantages of this apparatus are that it is of simple construction; the needle is always in view when inserting it; it can be held comfortably and firmly in place. The end of the block prevents the needle from entering too far and serves as a fulcrum upon which the block turns, automatically causing the needle to assume a plane in the direction of the sinus. The beveled surface lying flat against the scalp prevents lateral movement and keeps the needle in a constant position. Any ordinary needle with a short bevel up to an 18 gage can be used.

I am indebted to the Randall-Faichney Company, Boston, for the manufacture of the apparatus.

CLINICAL DEPARTMENT

CASE OF MENINGITIS DUE TO THE BACILLUS ACIDI-LACTICI

OCCURRING IN A PREMATURE INFANT ONE MONTH OLD *

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ANN ARBOR, MICH.

The occurrence of meningitis in the new-born and infants under three months of age is said to be uncommon. Barron,[1] in 1918, was able to collect only thirty-nine cases. Of these fourteen were due to the colon bacillus. It was thought that the report of an additional case would prove of interest, especially as the causative agent was the *Bacillus acidi-lactici*. In a search of the literature I can find no mention of this organism causing a meningitis.

REPORT OF CASE

L. P., a negro girl, aged 1 month, was admitted to the pediatric service of the New York Nursery and Child's Hospital, April 16, 1920. Chief complaint convulsions followed by stupor.

Family History.—Mother died of tuberculosis two weeks after the birth of the patient.

Birth History.—Child was born prematurely at seven months. Birth weight, 4 pounds.

Feeding History.—Has been receiving a skimmed milk mixture. Details unknown.

Past Illness.—None.

Present Illness.—Seven days prior to entrance the baby began to refuse its feedings and appeared ill. No fever noticed at this time. Five days later the patient had two generalized convulsions, each lasting about five minutes. There had been no vomiting at any time. No stiffness of the neck nor any retraction were noticed. The baby had gradually become more apathetic, and for the last twenty-four hours was stuporous.

Physical Examination.—Patient is a very poorly nourished negro infant nearly moribund. Lies in a stupor with eyes half closed. Respirations very shallow and irregular. Cannot be aroused to notice objects. Anterior fontanel is very tense and bulging. Pupils contracted; equal; react very sluggishly to light. No discharge from external auditory canals. Tympanic membranes cannot be seen. Tongue and mucous membranes very dry and covered with thrush. No rigidity of neck, nor any retraction. Heart sounds are very rapid, no murmurs heard. Few coarse râles heard over bases of both lungs. Abdomen

* Received for publication Sept. 23, 1920.

* From the Pediatric Service of the New York Nursery and Child's Hospital (Dr. Oscar M. Schloss, director) and the Department of Pediatrics, Cornell University.

1. Barron: Am. J. M. Sc. **156**:365, 1918.

is sunken; spleen not felt. No Kernig or Brudzinski. Tache cérébrale not present. The skin shows evidence of moderate dehydration. Temperature, 98.4 F. Weight, 4 pounds 13 ounces.

Laboratory Findings.—Leukocytes, 19,400. Polymorphonuclears, 58 per cent.; lymphocytes, 42 per cent. Urine specimen not obtained. Von Pirquet negative at twenty-one hours. Lumbar puncture: 10 c.c. of thick purulent fluid under moderate pressure. The fluid was pure white in color and on standing a short time gave the appearance of curdled milk. Globulin test, ++++. Sugar, negative. Stained smears showed the cells to be nearly all polymorphonuclear. Numerous gram-negative bacilli were seen, both intracellular and extracellular. The bacilli varied in size from long rods to coccoid forms.

Six hours later a ventricular puncture was performed and 35 c.c. of thin purulent fluid was withdrawn. Twenty c.c. of antimeningococcus serum was injected into the ventricles. Ventricular fluid: Cell count, 3,000 per c.mm.; 98 per cent polymorphonuclears. Globulin, ++. Sugar, negative. Stained smears showed the same gram-negative bacillus. The general condition of the patient grew steadily worse. Temperature rose to 106 F. Brownish bile-stained fluid was vomited. Continuous coarse twitching movements were noticed. Death occurred twenty-one hours after admission.

Necropsy.—(Seventeen hours after death) April 17, 1920. The body is that of a poorly nourished negro girl. Length, 19 inches. Weight, 4 pounds 14 ounces. The principal pathology is intracranial. The entire surface of the brain is covered with a thick greenish yellow exudate. This is more marked over the right side. The convolutions are entirely flattened out. Cut sections show marked congestion and edema. The ventricles are slightly dilated and filled with a thin purulent fluid. The right antrum and middle ear are filled with pus. Smears from the cortex and right middle ear show the same gram negative bacillus found in the spinal and ventricular fluids. The microscopic sections of the brain show a purulent lepto-meningitis with marked congestion and edema of the cortex. The rest of the examination was practically negative. There was no pneumonia, nor was any evidence of tuberculosis found. The bladder urine was negative for albumin and leukocytes.

Anatomic Diagnosis: Acute purulent leptomeningitis; acute purulent otitis media (right).

The Organism: Cultures from the spinal fluid obtained from the first lumbar puncture were made on plain nutrient agar and bouillon. The agar tubes showed a profuse moist spreading grayish growth in eighteen hours. The bouillon cultures became cloudy in nine hours. After eighteen hours the tubes were very cloudy with a marked sediment at the bottom. Smears from the agar and bouillon cultures showed a pure culture of a gram-negative coccoid bacillus. Hanging drop showed a motile bacillus.

Fermentation Reactions (courtesy of Dr. Harold Amoss of the Rockefeller Institute): Glucose, mannite, levulose and lactose were fermented with the production of gas and acid. Saccharose, inulin, dextrin and salicin were unattacked.

According to the classification of Kliger[2] and Levene,[3] the organism is the *Bacillus acidi-lactici*, one of the colon group.

COMMENT

The diagnosis of meningitis in very young infants is very difficult, the condition often being unsuspected during life. The only physical signs in this case were the stupor and bulging fontanel. The history of tuberculosis in the mother was suggestive of tuberculous meningitis

2. Kliger: J. Infect. Dis. **15**:187, 1914.
3. Levene: J. Bacteriol. **3**:253, 1918.

in the patient. After the lumbar puncture it was thought that we were dealing with a colon bacillus infection until the fermentation reactions were performed. However, the gross appearance of the spinal fluid was quite different from that usually described in colon meningitis (a dark brownish purulent fluid with an offensive odor). The fluid in this case was pure white in color, it had no odor, and on standing looked like curdled milk.

The portal of entry in this case was probably through the right middle ear. No other focus was found at necropsy. The causation of meningitis by an organism such as the *B. acidi lactici* can probably be explained by the fact that the patient, a premature infant, very poorly nourished, had not sufficient resistance to overcome even this ordinarily harmless saprophyte.

HEART DISPLACEMENT APPARENTLY DUE TO MEDIASTINAL EMPHYSEMA FOLLOWING ASPIRATION PNEUMONIA *

E. C. FLEISCHNER

SAN FRANCISCO

Heart displacement in children is ordinarily due to the presence either of free fluid or free air in the pleural cavity. The following case illustrates a marked type of displacement of the heart to the right in which neither pleuritic effusion, hydrothorax nor pneumothorax played a rôle.

REPORT OF CASE

G. P., aged 4 years, Sept. 10, 1919, at 4 p. m., fell into a pile of sand, and on being picked up by his mother stated that he had swallowed some of the sand. No effect was evident at that time, but when the boy was put to bed at 6 p. m., two hours after the accident, musical sounds were heard all over his chest, and he was breathing very rapidly.

He was taken to the Children's Hospital four hours after the accident, at which time physical examination revealed nothing beyond the presence of a large number of sibilant and sonorous râles over both lungs anteriorly and posteriorly. Roentgen-ray examination made one day after the accident was negative (Figure 1). Temperature and pulse were practically normal for about forty-eight hours. Five days after the aspiration of the sand, there were definite signs of bronchopneumonia on the left side, particularly over the middle lobe. Eight days after the accident, physical examination disclosed that the heart was very markedly displaced to the right. Roentgen-ray examination at that time showed a profuse bronchopneumonia of the left lung and the heart very markedly pushed to the right side (Figure 2). The explanation of this displacement was not apparent for six days. September 24, subcutaneous emphysema developed suddenly in the supraclavicular space on the right side, extending upward, backward and downward over the right lung posteriorly as far as the pelvis. On account of the very serious general condition of the child, roentgenogram was not taken at that time. The air under the skin was gradually absorbed. At the end of one week it was no longer apparent.

October 7, about two months after the accident, roentgen-ray examination revealed (Figure 3) the heart still markedly displaced to the right with a diffuse pneumonic process of the left lung, which at this time involved the lower lobe more than on previous examination. The patient continued to have a septic temperature; he coughed a great deal, and on physical examination, besides the heart displacement, showed diminished breathing all over the left lung, bronchovesicular in character, with a variety of adventitious sounds. He was returned to his home. His temperature became very much more septic in character; he emaciated more rapidly and expectorated large quantities of purulent sputum. Bronchiectasis was suspected. He was taken back to the hospital, a fourth roentgenogram (Figure 4) was taken which showed a diffuse bronchopneumonia still present with small bronchiectatic cavities.

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* Received for publication Oct. 6, 1920.

* From the Department of Pediatrics of the University of California Medical School.

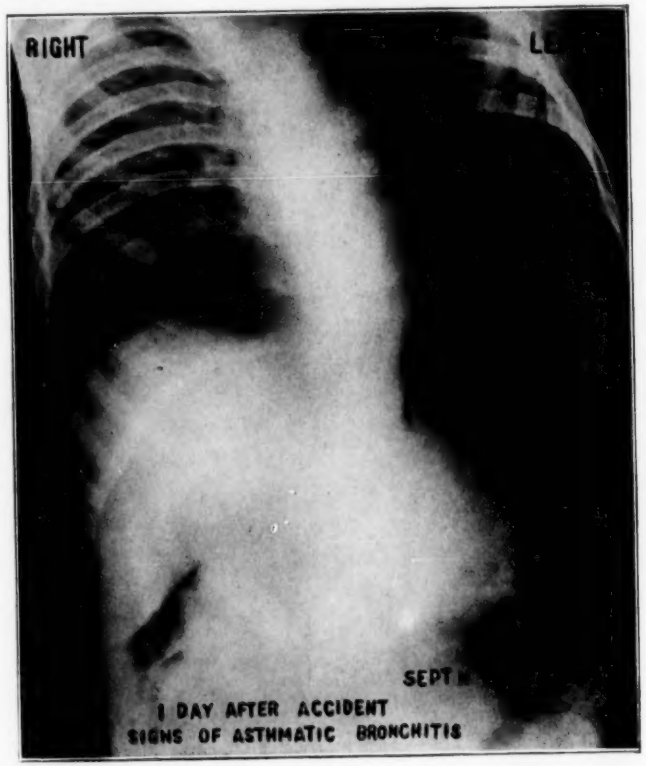

Figure 1

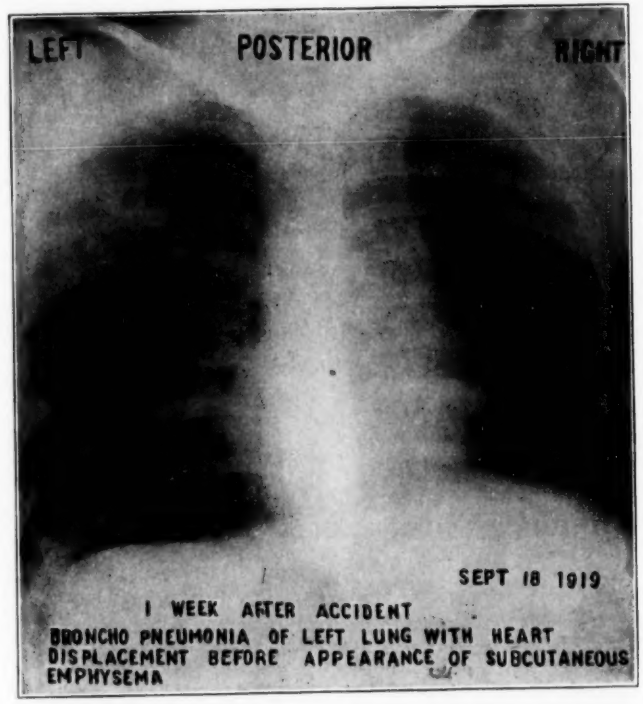

Figure 2

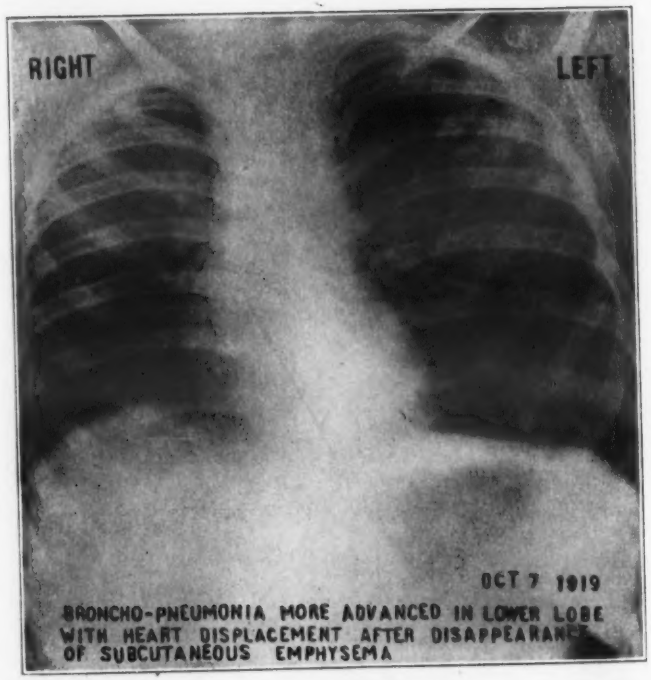

Figure 3

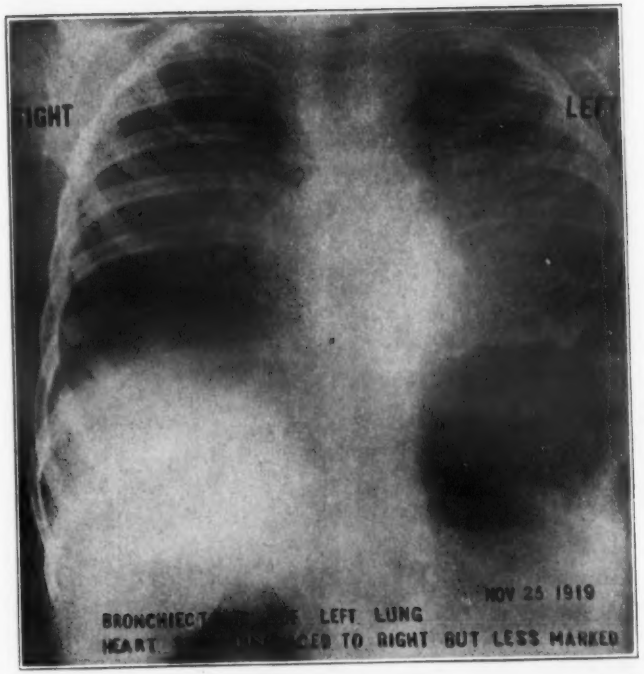

Figure 4

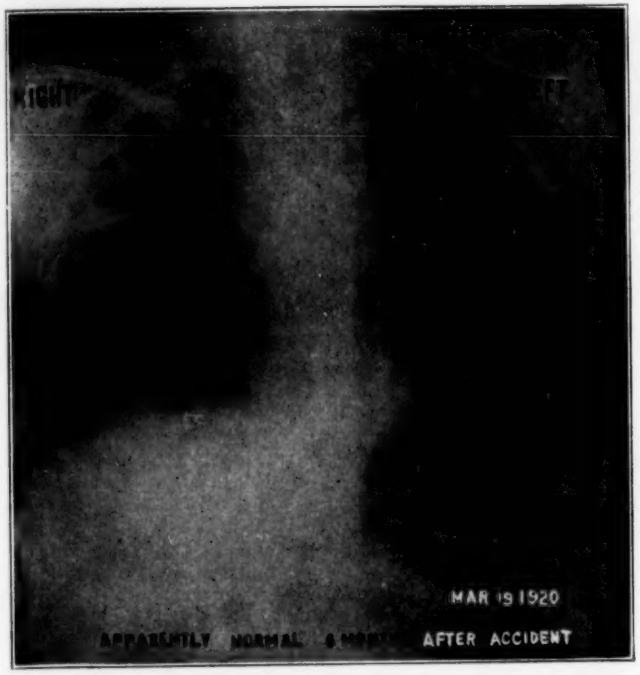

Figure 5

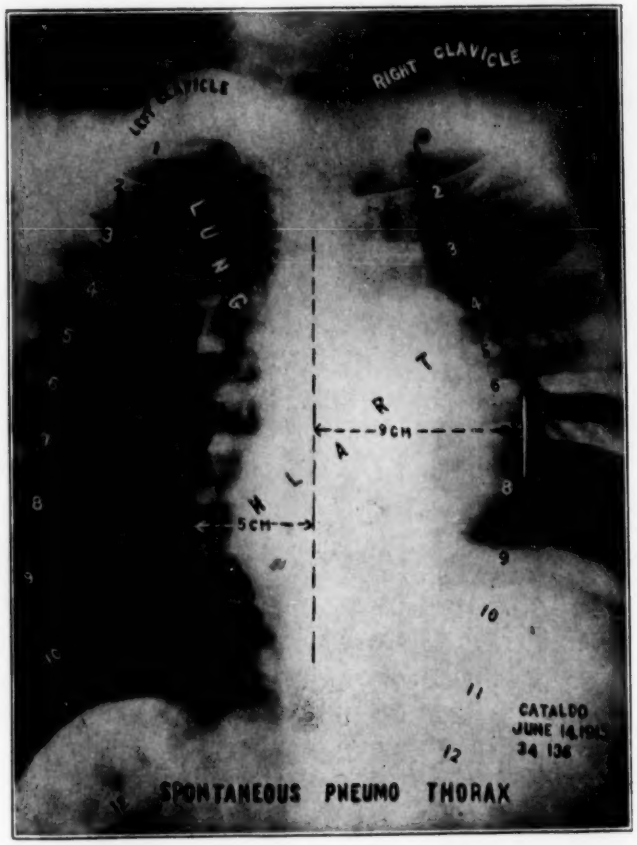

Figure 6

The child was then taken to the country and was not seen for several months. His temperature gardually reached normal, his cough diminished, the amount of sputum grew progressively less; he gained weight and was brought back March 19, 1920, about six months after the original accident. Physical examination was negative and the last roentgenogram (Figure 5) taken at that time showed an apparently normal chest.

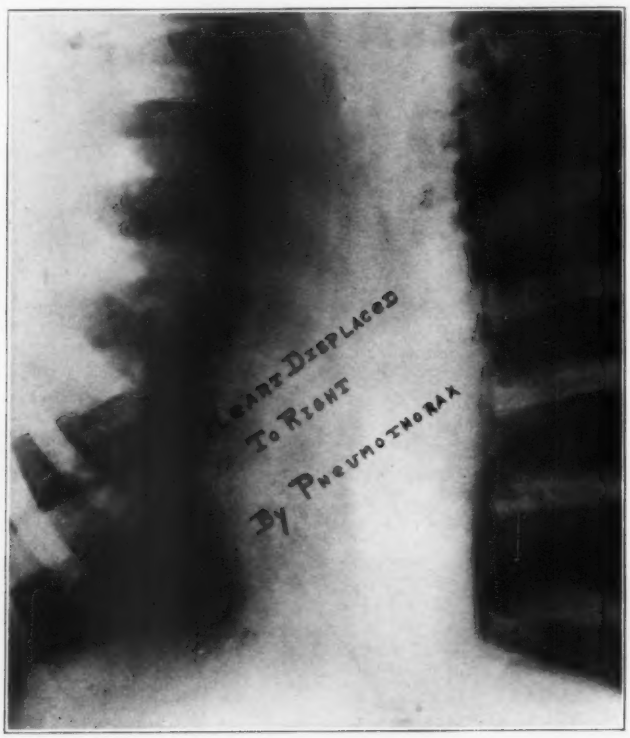

Figure 7

COMMENT

The case is essentially interesting on account of the marked displacement of the heart which was apparently due to the rupture of some of the air vesicles of the inflamed lung allowing free air to escape into the mediastinum, from which it made its way up under the right clavicle and posteriorly over the right side. Were it not for the fact that subcutaneous emphysema manifested itself, it would have been very difficult to have excluded an intense interstitial emphysema of the left lung as the cause of the displacement, but considering the fact that the air escaped from the inflamed lung and not having been able to prove its presence in the pleural cavity, one is forced to the conclusion that the heart could only have been displaced by the presence of air in fairly large quantities in the mediastinum.

A careful review of the literature fails to disclose any record of a similar observation.